



## MONTHLY DINNERS

Monthly dinners are held in the College on the Wednesday before the second Thursday of each month. The following are entitled to attend with their guests : All Diplomates and students of the College and Members of the Associations linked to the College through the Joint Secretariat. It is not necessarily intended that guests should be members of the medical profession.

The dinners will be at 7 p.m. on the following Wednesdays : October 12, November 9, and December 7, 1949, January 11, February 8, March 8, April 12, May 10 and June 7, 1950. There is an inclusive charge of £1 5s. (including drinks), which must be sent with the application to the Assistant Secretary at least a week before the date of the dinner. The dress is Lounge Suit or Uniform.

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### DIARY FOR SEPTEMBER (15th-27th)

Thur. 15	First Membership Examination begins.
Fri. 16	D.C.H. Examination begins.
Tues. 27	Final Membership Examination begins.

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### DIARY FOR OCTOBER

Mon. 3	General Surgery Lectures begin.
Tues. 4 11.00	PROF. J. BEATTIE—The Applied Physiology of the Kidney.
Wed. 5 11.00	PROF. J. BEATTIE—The Physiology of Micturition.
Fri. 7 5.00	DR. B. D. PULLINGER—Kettle Memorial Lecture.
Mon. 10	Basic Sciences Practical Demonstrations begin.
Mon. 17 10.00	MR. A. D. MARSTON—History of Anæsthesia.
11.15	MR. A. D. MARSTON—History of Anæsthesia.
5.00	DR. B. L. S. MURTAGH—Avoidable Accidents.
Tues. 18 10.15	DR. H. G. EPSTEIN—Physics in Anæsthesia.
11.30	DR. H. G. EPSTEIN—Physics in Anæsthesia.
5.00	DR. GEORGE EDWARDS—Pre-operative Medication.
Wed. 19 10.00	DR. E. S. ROWBOTHAM—Continuous Spinal Analgesia.
11.15	PROF. E. A. PASK—Respiration.
5.00	PROF. E. A. PASK—Respiration.
Thur. 20 10.00	PROF. E. A. PASK—Circulation.
11.15	PROF. E. A. PASK—Circulation.
5.00	DR. JOHN HEWER—Anæsthesia for Neurosurgery.
5.00	PROF. V. DIX—The Conservative Treatment of Hydro-nephrosis.

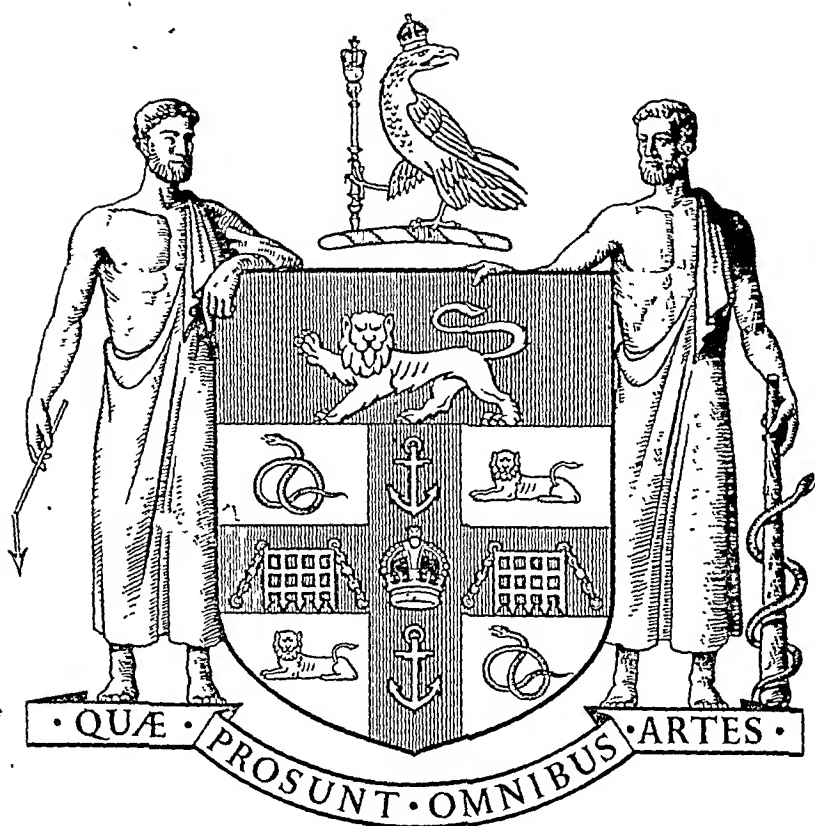


# ANNALS OF THE ROYAL COLLEGE OF SURGEONS OF ENGLAND

EDITOR: SIR CECIL WAKELEY, K.B.E., C.B., D.Sc., P.R.C.S., F.R.S.E.

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- (1) Pancreatic œdema and mild cases of acute hæmorrhagic pancreatitis.
- (2) Cases seen late and in which there is a certain recovery of function.
- (3) Widespread and apparently total glandular destruction.

In 10 out of 25 established cases in which this test was employed, the results were within normal limits.

In one of these cases in which it was increased, the diastase index was 600 units per cc. representing a daily output of diastase of 336,000 units. An increased urinary diastase is not, however, pathognomonic of acute pancreatitis because, although it never reaches very high figures, it may rise to 200 units per cc. in carcinoma of the head of the pancreas due to obstruction of the ducts, and toxæmia of pregnancy due to increased permeability of the kidneys.

*Oliguria* occurs only in very severe cases and may even amount to a definite anuria. It is usually attributed to low blood pressure causing impaired renal circulation or pressure of the pancreas on the renal veins causing marked renal congestion.

### BLOOD CHANGES

(a) *Blood Diastase*.—The range of normal levels is usually given as 60-200 units of diastase per cc. of serum and there is now no doubt that a rise of serum amylase is almost invariably associated with pancreatic disease and if it is over 1,000 units per cc. the prognosis is said to be bad. I do not support this view regarding the prognosis unless the level remains persistently high over a period of 24-72 hours. The highest figures are usually found within 12 hours of the acute attack and the vast majority have returned to normal by the 6th-10th day. It must not be forgotten, however, that a definite case of acute pancreatitis may have a normal blood diastase. This usually indicates, if the clinical condition is satisfactory, that the pancreatitis is subsiding or has subsided.

In this series, the blood diastase was estimated in 23 cases (20·9 per cent.) at times varying from 4 hours to 8 days after the onset of symptoms. In 14 cases (12·7 per cent.) figures over 1,000 units per cc. all occurred within four days of the onset and all except one had returned to normal within five days. In five cases (4·5 per cent.) there was no rise in the serum amylase.

Other conditions which may give rise to increased blood diastase are :—

- (1) Parotitis.
- (2) Renal disease.
- (3) Trauma to pancreatic gland.
- (4) Pancreatic cysts.
- (5) Carcinoma of head of pancreas.
- (6) Chronic venous congestion.
- (7) Diabetes Mellitus (rarely).

It will be noted that only two acute surgical conditions, namely, acute pancreatitis and trauma to the pancreatic gland are accompanied by an



## ACUTE PANCREATITIS

at this juncture. In some cases, after the acute onset, the symptoms subside, but the pulse rate remains high and a mass develops in the epigastric region. This is followed by localised suppuration or sloughing of the gland. In the suppurative form, the pus may (1) collect in the substance of the pancreas, (2) fill up the lesser sac and bulge beneath the left vault of the diaphragm, or (3) present in the left lumbar region and simulate perinephric abscess.

In the later stages, when there is no localisation, there are signs of diffuse peritonitis with free fluid or retroperitoneal cellulitis.

The symptoms of sepsis usually develop after 7-10 days and ultimate recovery after prolonged illness may follow rupture of an abscess into the bowel. Perforation into the peritoneal cavity, stomach or duodenum may occur. Temporary improvement may end in late death in 4-6 weeks after operation from pancreatic insufficiency. The symptoms then are malnutrition, wasting, profound weakness, hypotension, hypoproteinaemia, glossitis, vitamin D and vitamin K deficiency, fatty diarrhoea and uncontrollable vomiting of small amounts. Death may also be due to hæmorrhage from neighbouring vessels or to septic absorption.

Gangrenous pancreatitis may follow (1) hæmorrhagic or suppurative infiltration of the pancreas, (2) trauma, or (3) perforated gastric ulcer. The symptoms of hæmorrhagic pancreatitis may precede or be associated with it, and death usually occurs in 10-20 days.

### DIFFERENTIAL DIAGNOSIS

TABLE 7

Diagnosis by General Practitioner	Number of Cases	Percentage
(1) Acute Abdominal Pain .. ..	43	39.1
(2) Acute Cholecystitis .. ..	23	20.9
(3) Acute Intestinal Obstruction ..	14	12.7
(4) Perforated Peptic Ulcer .. ..	8	7.3
(5) Peritonitis .. ..	6	5.5
(6) Coronary Thrombosis .. ..	5	4.5
(7) Acute Appendicitis .. ..	5	4.5
(8) Acute Gastritis .. ..	2	1.8
(9) Acute Pancreatitis .. ..	4	3.6

A diagnosis of acute cholecystitis in 23 cases (20.9 per cent.) was probably due to the fact that these cases exhibited a history of gall-bladder disease whilst 13 cases (11.8 per cent.) showed some degree of jaundice.

A history of recent constipation and the presence of repeated vomiting has undoubtedly played a part in arriving at a diagnosis of acute intestinal obstruction which was given in 14 cases (12.7 per cent.) of this series.

A correct diagnosis was made in only 4 of the series (3.6 per cent.). On admission to hospital the surgeon made a correct diagnosis in only 46 cases (41.8 per cent.), whilst the other possible diagnoses are tabulated on the following page.

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(26·8 per cent.) died. Post-mortem examination was performed on each of these 11 patients and the diagnosis was confirmed. Of these 11 patients, 3 died within 24 hours of admission, whilst 4 more died within 5 days. The post-mortem findings were interesting and are detailed as follows :— in 3 cases the gall-bladder and bile ducts were found to be perfectly healthy, whilst in 8 cases chronic cholecystitis was present, 4 of these also having gall stones. In 2 cases, with cholelithiasis, a stone was found in the ampulla of Vater. In one case the peritoneal cavity contained one pint of straw-coloured fluid and the upper part of the duodenum was markedly dilated. Five cases showed fat necrosis and 2 cases had thrombosis of the splenic vein.

### Shock

This is not the appropriate occasion to describe the classical signs and treatment of shock, but a few points on its treatment as related to this disease are worth recording.

(i) *Transfusion and Infusion*.—As pointed out by Jensenn (1946) the plasma given by transfusion may pass into the serous cavities irritated by the pancreatic secretions and may therefore account for the cyanosis and shock with hæmoconcentration. In certain cases transfusion of whole blood is indicated to counteract that lost during the hæmorrhagic phase.

If the patient is dehydrated from repeated vomiting, intravenous saline with 5 per cent. glucose should be administered. A word of warning must be given here because large doses of intravenous glucose may be dangerous. Experimentally it has been shown that an elevation of the blood sugar level causes an increased flow of pancreatic juices rich in ferments. This may be counteracted in humans to a certain extent by giving one unit of insulin for each four grammes of glucose.

(ii) *Drugs*.—As stated previously, I do not advocate the use of morphia for the relief of pain in acute pancreatitis because although it will do so in full doses by its action on the central nervous system, at the same time it causes further spasm, or at least increases the tone of the smooth muscle. This would cause a contraction of the sphincter of Oddi with a resulting rise in the biliary and pancreatic pressures and possibly further damage to the liver and pancreas. I therefore advise the administration of anti-spasmodics because not only is the pain diminished or abolished, but a stone or plug of mucus in the ampulla of Vater, if present, can be passed into the duodenum by the relaxation of the sphincter whilst it also produces a fall in the intra-ductal pressures.

Immediate, although only very temporary, relief can be obtained by giving inhalations of amyl nitrate, but a better method is to give tablets of nitroglycerine to suck or chew. Papaverine or Eupaverin give more prolonged effects, and ephedrine, either alone or in combination with atropin and papaverine, is excellent. Papaverine may also be of value for its vaso-dilator effect because the extent of local vasoconstriction may

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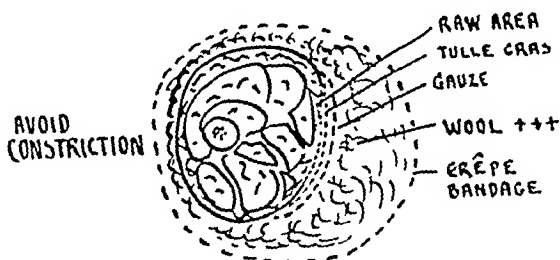
Cameron *et al.* (1945) have demonstrated that delay in the application of pressure detracts from the advantages.

The disadvantages—in some ways additional advantages—are (1) experience of the details of the method is required; and (2) careful attention is demanded for 48 hours.

Some authorities consider preliminary plenary treatment unnecessary, but most consider the step beneficial. In extensive burns the writer omits the cleansing and combines the immediate application of pressure dressings with absolute immobilization by splinting.

The burn is covered with a bland dressing, such as tulle gras (vaseline open mesh gauze) followed in turn by several layers of dry gauze, very liberal quantities of teased-out wool and fixation with crêpe bandages to ensure even pressure. The compression must provide moderate tension only, must be uniform and must not cause constriction (Fig. 1).

### PRESSURE DRESSING



COMBINED WITH ELEVATION  
AND IF POSSIBLE WITH A LIGHT PLASTER  
OF PARIS CASE FOR IMMOBILIZATION

Fig. 1. Constituent parts of a pressure dressing for burns.

A plaster slab is then applied to ensure immobilization and to render elevation—e.g., of a limb—easier. In burns of both aspects of the trunk and/or abdomen, pressure dressings are applied in a similar manner and the part immobilized with plaster of Paris.

In burns of the lower extremities and buttocks, following the employment of pressure dressings, a double light hip spica is applied. The nursing care of burns of trunk, buttocks and thighs is most readily carried out with the patient on a Bradford frame, with an opening in the covering webbing for the buttocks. In children the narrow ends of the frame can be slung to the top and bottom of the bed framework, bedpans can then be placed readily in position and contamination avoided. Further, this hammock-like position is enjoyed by the young patients who can indulge in "swings" to their liking (Fig. 2.).

The initial pressure dressings are not disturbed for 14 days, by which time superficial burns are healed while deep burns are ready for removal of sloughs prior to grafting. Cultures are taken from any raw area.



# THE SURGICAL MANIFESTATIONS OF SARCOIDOSIS

Erasmus Wilson Lecture delivered at the Royal College of Surgeons of England  
on  
10th March, 1948  
by

Ronald W. Raven, O.B.E., F.R.C.S.

Surgeon, Westminster Hospital (Gordon Hospital), Surgeon, Royal Cancer Hospital

THE SUBJECT OF sarcoidosis must have attracted the attention of Sir Erasmus Wilson, by whom this lectureship was founded, and who showed such a keen interest in the pathology of diseases which affect the skin. My own interest was kindled when a patient came under my care with an obstructive lesion of the ascending colon which was considered to be a carcinoma, but histological studies after a right hemicolectomy proved it as sarcoid. A study was then undertaken of the literature, revealing the experience of others, when it became apparent that sarcoidosis has attracted considerable attention from our profession, and this interest has grown during recent years. There is no reason to suppose that the incidence of the disease is greater, but more clinicians are now aware of many of its manifestations. This accumulation of data has occurred in a rather disjointed manner, for the literature is full of accounts of the disease as it affects the skin, the bones, lymphatic system, or other regions of the body. It is necessary to recognise that sarcoidosis is a single pathological process, a general systemic disease, which expresses itself by various clinical syndromes. Another matter which has received over-emphasis is the benign nature of the disease; this is erroneous as shown by the fact that about one-half of the autopsy cases reported died as a direct consequence of the disease. In addition to these interesting aspects of sarcoidosis, a great controversy has raged concerning the ætiology, and whether it should be regarded as a form of non-caseating tuberculosis.

The surgeon, therefore, cannot remain detached from this sphere so pregnant with speculative thought: indeed, there is a contribution for him to make. There remain certain clinical manifestations of the disease which require more elucidation, and the surgical implications of some of the clinical syndromes must be recognised in order that surgical treatment can be carried out.

## THE HISTORICAL BACKGROUND

In the development of our knowledge of this disease important contributions have been made by a number of investigators who are brought into the picture in chronological order.

1869. *Jonathan Hutchinson* has bequeathed to us in ten volumes, described as "Archives of Surgery," a monumental work of original and tireless observation written entirely by himself and comparable with those of John Hunter. He is the first to describe a form of skin disease which has "hitherto escaped special recognition. It may not improbably

## TREATMENT OF BURNS

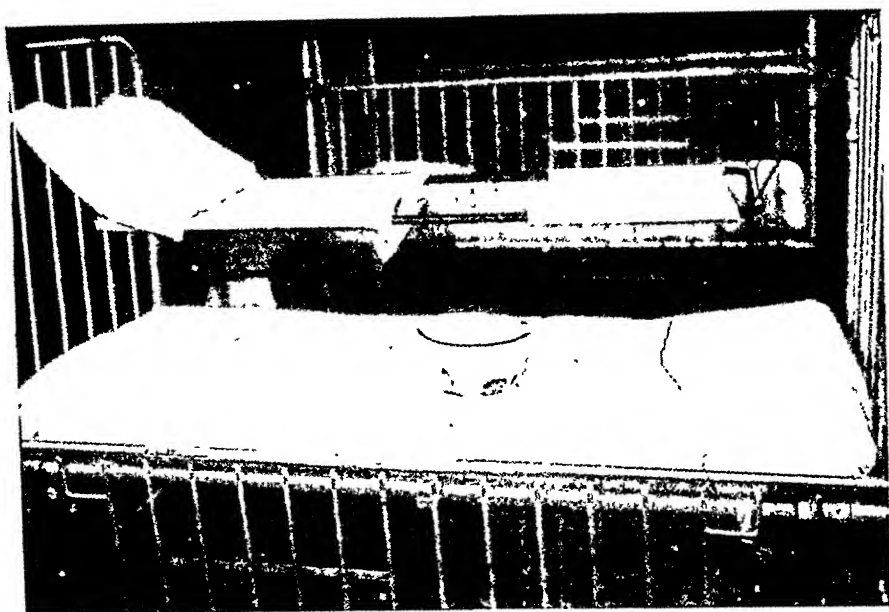


Fig. 2. Modified Bradford spinal frame suspended to bed framework for ease of nursing care in certain burns.



Fig. 3. Pressure dressing to burn of the hand. (a) Vaseline bandage to individual fingers. (b) Light bandage to fingers and palm. (c) Pad of wool to palm and palmar aspect of fingers. (d) Crêpe bandage fixation to gain necessary pressure.

be a tuberculous affection and one of the lupus family, but if so it differs from all other forms of lupus, both in its features and course. The disease is characterised by the formation of multiple, raised, dusty-red patches, irregular in size and shape, with sharp margins and smooth surfaces, neither painful nor tender and showing no tendency to inflammation or ulceration." A chromolithograph of the patient's hand was published and he noted that medicine of various sorts had no effect on the disease. In contra-distinction to modern practice Hutchinson stated: "I prefer to recognise it by the name of its subject as Mortimer's Malady." He then described a visit to Christiana in the summer of 1869 when "Dr. Bidenkop was kind enough to show me the collection of pathological drawings in the University Museum, and amongst these was one taken from a patient of Professor Boeck, showing a precisely similar condition of things to that delineated in my portrait. Professor Boeck told me that it was the only example of its kind that he had ever seen. The general opinion was, I believe, that the disease was sarcoma, and it was strongly urged that portions should be removed for microscopical examination. This was subsequently suggested to the patient and with the result that I did not see her again for two years."

1889. *Besnier* described a lesion of the skin involving the face, nose, and ears, which he named *Lupus Pernio*.

1892. *Tennessee* reported a similar case.



Sir Jonathan Hutchinson



Professor Cæsar Boeck

1899. *Cæsar Boeck*, a nephew of Professor Boeck, whom Hutchinson met at Christiana in 1869, described the morbid histology of the skin

# THE TREATMENT OF ADVANCED PARODONTAL DISEASE

Lecture delivered at the Royal College of Surgeons of England

on

3rd March, 1948

by .

Dr. E. Wilfred Fish, C.B.E., M.D., D.Sc., F.D.S.R.C.S.

ADVANCED PARODONTAL DISEASE may be defined for the purpose of these notes as that stage in the progressive destruction of the attachment of the teeth where deep pockets have appeared and so much of the attachment has been destroyed that the teeth have become loosened and may already have moved out of their original relationship and position. That is to say, advanced parodontal disease is characterized by an excessive depth of the pocket and loosening and displacement of the teeth (Fig. 1). In these patients several teeth have often been lost already or are unsavable so that the treatment of the case is complicated by the problem of their replacement.

Most of these cases are treated by total extraction, and economically this is the only possibility open to the vast majority of people in the present state of social evolution. The ultimate solution of the problem on a national scale is to prevent such extreme breakdown by proper instruction and supervision of the child and adolescent ; but, meanwhile, to grapple conservatively with the disease in its most advanced form may be the best way of gaining a real working knowledge of its pathology and of the factors which contribute to its causation and extension.

The parodontal attachment is destroyed by two agencies: one toxic, one mechanical. It is first attacked by the toxic products of the chronic marginal ulcers so prevalent in all who eat soft civilized food. The attachment of the epithelium to the enamel softens and gives way, so that the gingival sulcus deepens. The ulceration then spreads to the subgingival epithelium and the proteolytic breakdown products of these subgingival ulcers destroy the parodontal fibres and cause resorption of the bony alveolar crests.

When part of the bony socket and a certain proportion of the parodontal fibres have been destroyed the second phase sets in. The tooth becoming slightly loose, an additional strain is placed on those fibres and on that amount of bony support which remains. This strain itself then causes further bone resorption and continuing destruction. Naturally, teeth whose roots are short by nature tend to loosen more rapidly than those with long roots, and the prognosis of a case depends, therefore, as much on the length of the root as upon the depth of the pocket.

In order to follow the rationale of treatment it is necessary to refer briefly to the fundamental pathology of bone.

It will, perhaps, be generally agreed that the reaction of bone to irritation, whether mechanical or toxic, depends on the degree of irritation to which

lesion and stated : " The only clinical description known to me which bears any resemblance to my case is given in a recent paper by Jonathan Hutchinson in his Archives of Surgery, October, 1898. I dare not say that the skin affection there described as Mortimer's Malady is identical with my case, since the latter shows some very marked clinical features not found in Mortimer's Disease. Nevertheless, I am inclined to believe that they are only variant types of the same group of diseases and perhaps later on they may be found to represent benign forms of so-called pseudoleucemic affections of the skin." Boeck called attention to widespread involvement of lymph nodes with a yellowish-brown substance, and concluded, " as a preliminary name for the clinical and histological type here described the term " multiple benign sarkoid " perhaps will not be found unsuitable. History has proved that Boeck's last assumption was most unsuitable and a new nomenclature is very desirable.

1904. *Kreibich* published a short and accurate description of the radiological appearances of the hands in a case of lupus pernio. This was the first occasion when bone changes were associated with the disease.

1909. *Heerfordt* described the uveoparotid syndrome based on a study of cases in the Copenhagen City Hospital. This communication was followed by a number of case reports, chiefly from Scandinavian and German sources.

1914. *Schaumann* stressed that the disease had a predilection for lymphoid tissue and demonstrated that lymph node lesions were identical with those of the skin. He gave the name lymphogranuloma benignum and suggested that an underlying unity existed amongst apparently unrelated clinical entities.

1915. *Kuznitsky and Bittorf* focused attention on the pulmonary manifestations.

1919. *Jungling* proved by histological examination the exact relationship between the lesions in the bones of the hands and the skin lesions. He designated these osseous changes as osteitis tuberculosa multiplex cystica.

### TERMINOLOGY AND CLASSIFICATION

No other disease has been more beclouded by a multiplicity of designations than sarcoidosis. Hutchinson applied the name of the patient to the specific lesion in the skin and since that time many synonyms have been used. These include multiple benign sarcoid ; multiple benign lupoid ; sarcoidosis ; Hutchinson's, Boeck's, Besnier's, Tenneson's and Schaumann's disease (or combinations of these names) ; miliary lupoid ; lupus pernio ; benign lymphogranulomatosis ; or non-caseating tuberculosis. The term sarcoid or sarcoidosis has nothing to recommend it except that it is widely known : in fact, it is misleading.

Differentiation of the various manifestations of the disease is no longer tenable ; all the facts suggest that we are dealing with a disease entity which can affect any organ in the body. Thus there is a common ætiological factor capable of stimulating tissue reactions, especially in certain

and pointed, short-bladed scissors set at various angles, or in some cases with the gingivectomy knife and ordinary Howe's scalers with which the tartar can also be removed. Small curettes like large caries excavators are useful for the rounded masses of granulation tissue such as that shown in Fig. 2. but it is never wise to disturb the bone itself. If left undisturbed the bone is always free from infection; but if it is scraped or chipped away the resultant surface undergoes necrosis and exfoliation, thereby diminishing still further the attachment of the tooth.

Another important factor in producing rapid healing with a minimum of granulation tissue is careful and reasonably firm packing with the Zinc Oxide-Eugenol mixture on cotton wool. Each piece of packing should be carefully applied and any irregular space left by the excision of granulation tissue must be filled with the dressing and kept packed until it has epithelialised over. If this be neglected new granulation tissue will spring up and the case relapse. Epithelialisation may take two weeks in a severe case, and in that event the packs should be changed at the end of the first week.

Before passing on to the question of post-operative treatment some further reference must be made to the acute parodontal abscess. This condition often occurs with no greater discomfort to the patient than a little tenderness of the tooth on percussion so that no advice is sought and it is soon forgotten. The evidence of its occurrence remains, however, as a closely localised pocket or deepening of the sulcus at that particular point on the circumference of the root of the tooth where the abscess bursts into the gingival trough. If, however, the abscess is more deeply placed it can be extremely painful and call for prompt relief. Often it has already pointed into the sulcus or on to the surface of the gum nearby, or it may be opened almost accidentally when gently exploring the sulcus with a blunt probe. Alternatively, the only evidence of the presence of the abscess may be that the tooth is exquisitely tender to percussion, and even sensitive to heat if the abscess is near enough to the apex to cause congestion of the pulp.

The treatment depends upon the severity of the symptoms and whether the pus can be evacuated or not. If the abscess has already pointed, and if the symptoms are slight and the tooth is reasonably firm, a course of penicillin over a few days will get rid of the acute symptoms. Five hundred thousand units of penicillin injected intramuscularly twice daily should be adequate, together with very hot mouth washes, held in the mouth as long and as often as possible. Even if extraction is contemplated it is better to delay opening up the surrounding bone in the presence of acute sepsis provided the pus has an outlet and the inflammation is subsiding. Of course, if the pus cannot otherwise be evacuated and the pain is severe, the tooth must be extracted; but once the acute phase has passed it is remarkable how many of these parodontal abscesses prove to be amenable to excision without loss of the tooth.

regions, including the skin, lymphatic system, hæmopoietic tissues, bone and viscera. The evidence suggests that the tubercle bacillus fulfils these conditions and when this concept is finally accepted, the best designation will be non-caseating tuberculosis. In the meantime the term sarcoidosis is retained.

#### THE DISEASE PATTERN

Sarcoidosis may affect almost every tissue in the body, but possesses a predilection for certain structures so that a disease pattern is presented. The commonest sites include the lung, lymph nodes, skin, eyes, spleen, liver and bone. It is of interest to note that hæmatogenous tuberculosis possesses a similar pattern of distribution.

#### THE CHARACTERISTIC PATHOLOGICAL LESION

The pathological lesion is characteristic and the appearance on microscopy is the same wherever the disease is situated (Fig. 1).

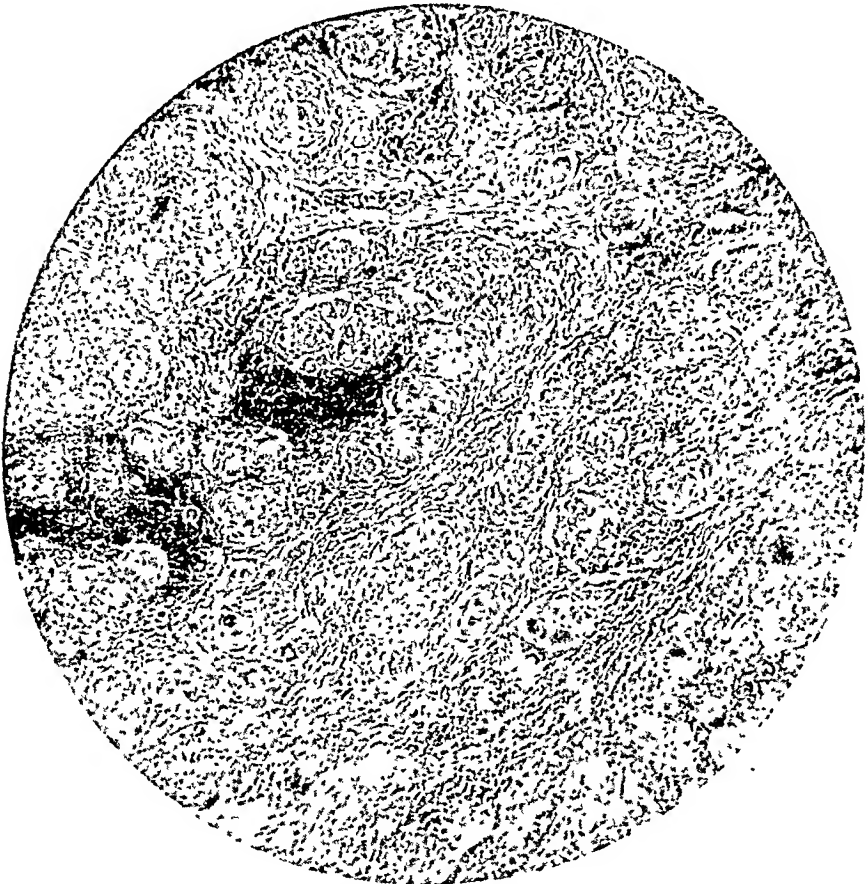


Fig. 1. Low-power photomicrograph of part of a lymph node showing an extensive deposit of sarcoidosis. The microscopic picture is characteristic, and shows rounded and lobulated masses of reticulo-endothelial cells associated with small multi-nucleated giant cells, the distribution of whose nuclei is mainly peripheral. Many of these unit masses have become confluent, thus largely replacing the normal lymphadenoid parenchyma.

might have precipitated a parodontal abscess. Caries, however, has usually ceased to be such a pressing problem at the age when a parodontal splint becomes necessary and this patient was well over forty.

One other problem remained ; the splint could only be left out at night provided that some other simple plastic cap was worn over a few premolars to prevent the bite closing and so moving the retracted central out again ; but as an alternative two " high " inlays were put in the lower first molars and they were accommodated occlusally in the splint.

It may be suggested that this patient might regard the splint as an unwarrantable infliction, but in fact that is not the case ; it did not show and it gave her great support and comfort in mastication. The alternative was extraction of that ugly tooth, and a bridge, or a plate. The bridge would in any case have soon led to a plate, so she was only anticipating this event by a little time and meanwhile she enjoyed the advantage that she could remove the splint, as she did every night, and could retain her front tooth indefinitely.

This case is now an old story and it has progressed through the years very favourably, but it has been described in some detail because it presents in a challenging way this problem of tooth wandering under occlusal stress in cases of advanced parodontal destruction. It was the starting point in the evolution of a principle in splint design which is incorporated now in every partial prosthesis for which one is responsible. The occlusal surfaces of all the remaining teeth in all these cases are covered with gold and each is thus supported by all its neighbours against occlusal trauma.

To turn, therefore, to more general considerations, the tendency to wander is much more marked in the upper teeth than in the lower ones because the upper arch is outside the lower. Any arch can resist compression, provided the teeth are all in contact, much more sturdily than it can withstand the disruptive effects of expansion which appear in the upper arch when the lower arch is driven up into it ; the lower arch is compressed and is unaffected ; the upper is expanded, and the teeth are spread.

Other factors influence the tendency of teeth to wander and are therefore to be taken into account when considering the indications for a parodontal splint. They are the length, contour and general sturdiness of the roots of the individual teeth, the strength and texture of the bone and its threshold of susceptibility to mechanical irritation beyond which resorption set in, the amount of parodontal attachment which has been destroyed by the chronic ulceration of the subgingival epithelium before treatment was instituted and the total number of teeth which remain to share the masticatory stress.

In many cases, as indeed in the one referred to at length above, only one, or perhaps two or three teeth have moved out of place ; or they may merely have loosened or only feel insecure. Where a tooth has moved it will be observed almost invariably that there is a very deep pocket, the product of a previous parodontal abscess on the side of the root from



It consists of a collection of large epithelioid cells which are arranged in follicles (Fig. 2). These follicles may be isolated structures in comparatively normal tissue or arranged in groups or strands (Fig. 3). Sometimes they attain to a considerable size and replace most of the normal tissue (Figs. 4 and 5). Occasionally a large pale-staining giant cell is found at the centre or periphery of these collections of cells.

An inflammatory reaction in the surrounding tissues is usually absent and there is no caseation although a few necrotic cells may be present in the centre. The lesion often remains unchanged for several years and healing may occur with fibrosis and hyalinization. The histological picture is that of a proliferative rather than an inflammatory process.

*Ætiology.* There has been a considerable amount of discussion regarding the causation of sarcoidosis and many theories are advanced by various authorities. Thus Kuznitsky and Bittorf consider it is a granuloma produced by a specific infection other than the tubercle bacillus. Kissmeyer and Nielsen call attention to the resemblance of the bone lesions to those found in leprosy, and suggest that some specific agent is the cause which is allied to the lepra bacillus, and produces a peculiar form of chronic granuloma different from either tuberculosis or leprosy. Williams and Nickerson postulate the presence of a filterable virus. Others have pointed out the analogy between sarcoidosis and lymphadenoma and it has been termed benign lymphogranuloma.

The major part of the discussion concerns the relationship of sarcoidosis and tuberculosis. The school of thought against the view that sarcoidosis is non-caseating tuberculosis bases its arguments on the facts that the tuberculin test is usually negative; that tubercle bacilli can rarely be demonstrated in the tissue by the microscope; and that inoculation of guinea pigs with sarcoid tissue will not produce a tuberculous lesion. However, these facts can be readily explained. The negative tuberculin test is accounted for by tissue anergy, a state of absolute immunity being produced. The tubercle bacillus is difficult to demonstrate in microscopical sections because it is of low virulence in these cases and has probably died when the typical lesion has appeared. Kyrle made observations on a case where the earliest lesions showed numerous tubercle bacilli; shortly afterwards only a few could be found, and later it was impossible to find any, although the lesions presented the typical appearance of sarcoidosis. The spirochaete pallida behaves similarly—it is present in large numbers in early syphilitic lesions but is found with the greatest difficulty in the late lesions.

There is a considerable weight of opinion in favour of the view that sarcoidosis is non-caseating tuberculosis and many English workers consider it to be due to the passage of moribund or dead tubercle bacilli into the circulation and producing generalised lesions. If we accept this theory it is a feasible explanation for the fairly typical characteristics of sarcoidosis and the close similarity of the sarcoids to other foreign body

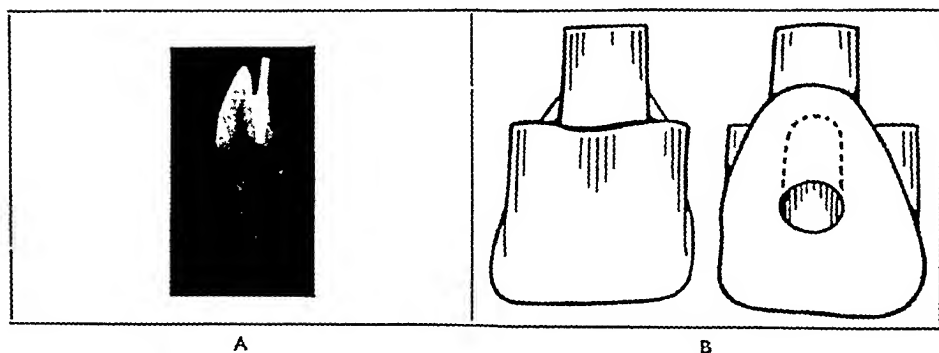


Fig. 3. (a) Lateral skiagram of the inlay in the case shown in Fig. 4 before removal of the sprue or drilling the hole for the pin.  
Fig. 3. (b) Sketches of the finished inlay.

lateral movement will in turn be prevented by the splint, through its attachment to other teeth. In this way loose teeth often become firm, but two commandments must be kept. The splint and the teeth must be scrupulously cleansed and the gum margins must be regularly and assiduously rubbed.

Perhaps, in conclusion, a few practical observations may be of use. It need scarcely be said that if only two or three loose teeth are left their united strength is not sufficient to stabilize either themselves or a prosthesis.

In the case of the lower splint, it is the splint rather than the teeth which is inherently weak, because it lacks the palatal bar of the upper splint and it may be necessary to carry it down over the lingual gum margin behind the incisors, but in that case the patient must be duly warned to pay very special attention to the gum margins that are covered and to give them extra friction with both brush and wood point. If the lower centrals are missing, as in Fig. 6, there is less difficulty because one can secure sufficient strength in the casting which is buried in the plastic of the incisors that replace the natural teeth. Otherwise the lingual bar, plus a modified continuous clasp design, may sometimes be used, but unless the incisors are inclined lingually, mastication is very liable to cause a roll of chronically inflamed gum margin to develop above the lingual bar. In any case the distal slope of the biting edge of the lower canine and the occlusal surfaces of the premolars and any other natural teeth, including even the incisors sometimes, must be covered by the casting. In this way, and apparently only in this way, is perfect occlusal support obtained to prevent the denture injuring the parodontal tissues. One very important warning should be given, and it is that the bite must never be more pronounced in the molar region than in the premolar region, or the patient will be quite unable to wear the appliance.

The value of this kind of design with its full occlusal support is particularly evident in cases where alternate teeth are lost and the remaining



Fig. 2. Low-power photomicrograph of a lymph node showing one solitary deposit of sarcoidosis, and a small confluent group of the same characteristic lesion. The peripheral distribution of the nuclei in the giant cells is well shown.



Fig. 3. High-power photomicrograph of a lymph node showing the margin of a deposit of sarcoidosis. This consists of a mass of reticulo-endothelial cells; an atypical giant cell is present towards the centre.

ones "interdigitate" when the mouth closes, since the whole weight of the bite is of course comfortably borne on the splints, and through them, on the remaining teeth. Another type of case where a splint is particularly useful is in a patient with very close bite despite the fact that all the teeth may be present. These patients may damage either the lingual upper gum margin or the labial lower gum margin by the bite of the opposing incisors, and parodontal abscesses may develop. Not a few of these people may develop Costen's syndrome. In either case a parodontal splint will relieve both the traumatic bite on the gum margin or the traumatic arthritis of the temporo-mandibular joints.

If it is the gum margins which are suffering, a lower splint, covering the occlusal and lingual surfaces of the posterior teeth and the lingual surfaces of the incisors, is the best choice since it frees the incisor bite entirely. In cases of Costen's syndrome an upper splint, opening the bite, permitting free lateral movement and having facets to provide an axial bite for the lower incisors, will give relief.

Finally, it is perhaps only a personal idiosyncrasy of the author, but he prefers to have these appliances made from a compensated sectional composition impression and cannot say whether they could be successfully built on any other.

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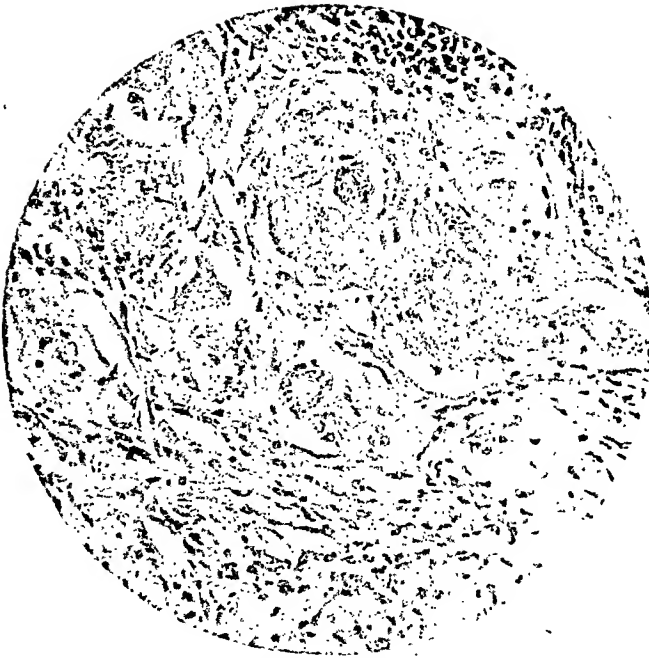


Fig. 4. High-power photomicrograph of a subcutaneous deposit of sarcoidosis. Typical confluent lesions composed of reticulo-endothelial cells are present. The giant cells show a peripheral distribution and extend completely around the circumference of the cell.

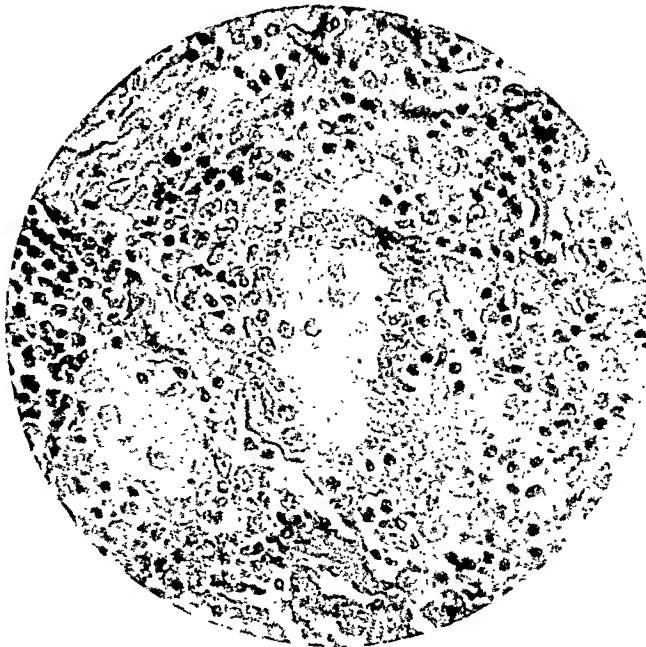


Fig. 5. High-power photomicrograph of part of a sarcoid lesion.

do not agree with the interpretations which were put on cystometrograms in the latter paper by Mr. Riches. Clinical and cystometric investigations of some 200 cases of urinary incontinence in children, whose ages range from  $2\frac{1}{2}$  to 14, have been carried out over a period of two years at St. Bartholomew's Hospital, the Hospital for Sick Children, Great Ormond Street, and the Sydenham Children's Hospital.

The problem of the enuretic child has been dealt with in many places by many people, and in England, the last great "mecca" on the subject was in 1944, again at the Royal Society of Medicine, Section of Urology.

The names of the late Oswald Addison, of Mr. Twistington Higgins and Mr. Winsbury-White, and, on the medical side, Dr. Wilfred Sheldon, have been associated with repeated attempts to keep this subject on a sane and practical level, but because of its tedium, its smell and its chronicity, enuresis keeps drifting to the vagaries of psychotherapy.

In common usage the word enuresis applies to urinary incontinence in the absence of organic pathology in either the nervous or the urinary systems. That is why I use the word incontinence, because (*vide infra*) 14 per cent. of the cases referred to me as enuresis had in fact gross relevant pathology. Thus, this distressing complaint should not be spelt enuresis. The word enuresis itself is derived from the Greek verb ἐνυρῶ, "I make water in"—and is not from εὑρισκω with its past tense derivation "I have discovered" (Fig. 1).

ἐνυρῶ.

E N U R E S I S

~~E N U R E S I S~~

Fig. 1.

### The Extent of the Problem of the Enuretic Child

The extent of the problem of the enuretic child is not adequately appreciated either by the profession or by the public. In 1948 a report was drawn up by the Joint Committee of the British Medical Association and the Magistrates' Association. This very authoritative committee suggests that one in seven of the total population have, at some time, suffered from nocturnal enuresis. They also assert that 85 per cent. of enuretics are suffering from disorders of function (undefined) and that approximately 8 per cent.—which they call the hard core—resist all treatment and are due to defective cerebral control. This 8 per cent.

reactions. The paucity of giant cells signifies that most of the offending organisms have been eliminated, and the presence of epithelioid cells is evidence that the focus is free from micro-organisms. Attention is also called to the development of sarcoidosis into tuberculosis, and it is the most frequent cause of death in cases of sarcoidosis. It is possible that reactivation of sarcoidosis into tuberculosis is caused by a diminution of resistance in the patient, or increased virulence of the bacteria. In any case it is extremely difficult to differentiate between these two diseases.

*The Clinical Picture.*—Females appear to be affected more often than males. The disease has been described in patients at the age of three weeks up to 70 years; the 30-40 age group is affected most frequently. Several authors have described the disease in sisters of different families. It tends to run a chronic course over a period of time varying from three to eight years, and there may be periods of remission from symptoms. Some patients develop tuberculosis with a fatal termination.

The clinical picture is variable, which is due to certain factors including the site of the disease, and the degree of progression or retrogression which is present. The absence of constitutional reaction, even in the presence of advanced disease, is often noticeable. There may be some degree of fever, malaise, anorexia, drowsiness, generalised aching pain, but usually there is no loss of weight. An unproductive cough may be present but the lack of symptoms in the presence of marked disease demonstrated radiologically is a striking feature. Enlargement of various groups of lymph nodes may be obvious on clinical or radiological examination. Skin lesions may be seen and an enlarged liver or spleen felt on abdominal examination. The features of eye involvement include puffiness of the eyelids, defective and failing visual acuity, and facial palsy or swelling of the parotid salivary glands may be present. Swelling of the fingers or toes, associated with pain, indicates bone involvement in these situations. Heart failure is present when there is diffuse pulmonary involvement, or severe infiltration of the heart. Other symptoms are manifested according to the distribution of the disease. It is pointed out that the symptomatology of sarcoidosis is caused primarily by mechanical interference with function rather than by toxic absorption; when the sarcoid lesions collect in large numbers, they tend to displace or destroy normal tissues, or tumours are produced which involve one or several organs.

### LABORATORY INVESTIGATIONS

*The Blood Changes:*—There may be a mild degree of anæmia. When fibrosis of the lung with emphysema occurs, polycythæmia may develop. The number of leucocytes is within normal limits or subnormal. A relative increase in the number of monocytes and eosinophils has been noted which may indicate a phase of active extension of the disease. This monocytosis may rise to more than 20 per cent.

In several cases also the bladder-filling sensation is defective but I am not certain about the significance of this. A chronically infected and distended bladder is often insensitive. Fig. 8 (d) shows the record from a boy who had chronic pyuria and stones. When the bladder is distended to a reasonable limit the child usually develops circum-oral pallor and begins to wriggle his toes, but there should still be no terminal rise in pressure. Such a terminal rise indicates a lack of control and is associated with urgency in the symptoms. Most children are able to check these bladder contractions by taking a few deep breaths. If this encouragement were not given to the children many of the contractions would have expelled the catheter. This deliberate attempt to control bladder contractions is the essence of bladder control in the aged, which has been so successful in geriatric centres. However, cystometry is not used as a method of treatment in children, although I think it has sometimes effected a cure.

### Consistency of Pattern

The pattern in the various groups is a consistent and constantly recurring one (Fig. 8). It might be thought that emotional factors while the examination is going on might well bring about abnormal behaviour

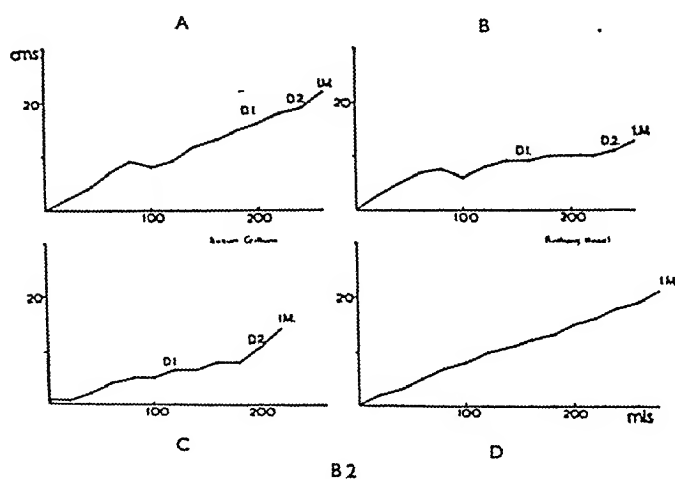


Fig. 8. Consistency of pattern in children of the same age; (a), (b) and (c) are enuretics and (d) pyuria.

on the part of the child and the bladder, but I do not believe that this is so. Fig. 9 is a recording taken during sleep. The reading awake was identical except that the capacity was a little less. The boy then fell



The total serum protein content may be increased, which is due to a rise in the globulin fraction ; the albumin-globulin ratio is consequently reversed. The serum calcium is either normal or raised ; during the active phase of the disease the serum phosphatase rises. The blood cholesterol is normal. The blood sedimentation rate is raised during the active phase of the disease.

*The Urine.*—This may be normal. Several authors have described sarcoid lesions in the kidneys associated with albuminuria and hæmaturia. Harrell found a substance resembling Bence-Jones proteose in the urine of two patients.

*Test for Sarcoidosis.*—This is not widely known in Britain. In 1941 Kolim demonstrated that a suspension of sarcoid tissue, sterilised by heat, taken from a proved case of sarcoidosis, could provoke a slowly forming, indolent papule when injected intracutaneously into a patient with the same disease. The sarcoid tissue is obtained from a lymph node. The papule will persist for several months and it may form an indolent ulcer. This test is stated to be very reliable.

*Treatment.*—Measures are instituted which will improve the general health of the patient and increase his resistance to the disease. Various empirical methods of treatment have also been used, including preparations of arsenic and iodides. Tuberculin and leprosal therapy have been given, and more recently calciferol is being used in doses of 50,000 units twice daily. With the latter treatment improvement in the skin lesions has occurred.

At the Royal Cancer Hospital a number of cases have been successfully treated with irradiation and illustrative examples are quoted.

*Case No. 1.*—Male, aged 23, seen with great enlargement of the mediastinal and hilar lymph nodes ; also some enlargement of supraclavicular lymph nodes—1 removed for histological examination and showed the characteristic features of sarcoidosis. Treated with high voltage X-irradiation, 200 kv. to mediastinal mass, dose maximum 1,400 r, minimum 1,000 r in 25 days. Six months later radiological examination showed complete regression of the mass, the patient was symptom-free, felt well and at work.

*Case No. 2.*—Female, aged 39, seen with an opacity at the root of the left lung and an enlarged mediastinal lymph node. A carcinoma of the lung was suspected but a biopsy of a supraclavicular lymph node showed the disease to be sarcoidosis. Patient treated with high voltage X-irradiation, 200 kv. to mediastinum, maximum dose 2,200 r, minimum dose 1,800 r ; to cervical nodes, maximum dose 1,700 r ; minimum dose 1,500 r. The mediastinal and cervical swellings disappeared and the patient remained well.

*Case No. 3.*—Female, aged 45, seen with a hard fixed mass occupying the upper half of the left side of the neck, with two smaller swellings behind it. There was some redness and fixation of the skin at the apex of the mass. Histological section showed sarcoidosis. Treatment was

motor and mental activity come to the fore. Training in the first two years appeared to have no influence on the later development of control.

### CYSTOMETRIC ANALYSIS

One hundred and fourteen cases were examined by cystometry, the youngest three and a half. Fig. 17 shows the analysis of 114 unselected cases from the functional group. It should be noted that 51 of them are normal. Many others show abnormal activity—that is uninhibited contractions, while a few (probably the British Medical Association and Magistrates' Association's hard core) show a persistence of the

STAGE	No.	%			
I	31	A.1	A.2	B.1	B.2
II	38	6.5	32	9.5	42
III & IV	17		10.5	37	47.5
VII	28		10.5	35	65
				32	57.5
TOTAL	114	3.5	15	30.5	51

### CYSTOMETRIC ANALYSIS

#### FUNCTIONAL GROUP

Fig. 17.

infantile type with small capacity and abnormal activity: that is cystometric groups A 1 and A 2. Whereas *Stages I and II* contain numerous uninhibited high tension types there is a progressive move to the right so that *Stages III and IV* are more mature. *Stage VII* cases, on the other hand, show a general mix-up as we would expect. It will be seen that the older the Bladder or Symptom Age the more normal the cystometric picture, and we can complete our staging chart by adding the cystometric groups to the symptom groups (Fig. 12).

I have already referred to the different types of contraction, some reaching consciousness, others unperceived, and to the fact that some bladders appear to lack the normal filling sensation.

### ORGANIC PATHOLOGY IN THE URINARY TRACT CONSIDERED CAUSATIVE OF INCONTINENCE

On returning to the organic side, in the whole series of 218 cases, 21 (10 per cent.) had gross urinary pathology in the urinary tract, sufficient in itself to account for the incontinence. Fig. 18 sets out the various causative factors. *It will be seen that over half were suffering from retention with overflow.*

given with teleradium using the 5 gm. unit, the dosage being 1,500 r. The swellings disappeared and the patient remained well.

Surgical treatment may be required for the relief of mechanical disturbances, especially of the gastro-intestinal tract.

More detailed consideration is now given of the manifestations of sarcoidosis in individual organs, some of which have a greater surgical significance than others. In the first instance the classical sites are dealt with, namely, the skin, lungs, lymph nodes and bones.

*The Skin.*—Skin manifestations are present in about 50 per cent. of cases and various types are described. The skin of the face, ears, nose and extremities is usually involved.

*The Papular Type.*—This occurs as an eruption of reddish papules which are smooth, sharply defined and of variable size. They are seen on the face, forehead, extensor aspects of the arms, buttocks and posterior part of the legs.

*The Nodular Type.*—These nodules are smooth, raised and red-blue and there may be telangiectasis on the surface. They vary in size up to 5 cm. and are usually situated on the face and extremities.

*The Infiltrative Type.*—This lesion is more diffuse with a sharp margin. It affects the nose, cheeks and lobes of the ears. The fingers are frequently affected and there are underlying bone changes present.

Another variety of infiltrative lesion is less common and seen on the lateral aspects of the root of the nose as soft infiltrating plaques which are violet-red and marked telangiectasis is present.

*The Erythrodermic Type.* Large superficial serpiginous areas develop on the anterior aspect of the thighs and legs, which are red in colour.

A single infiltrative type of cutaneous lesion must be differentiated from other similar lesions as seen in the tuberculoid variety of leprosy, leishmaniasis, syphilis and tuberculosis.

*The Lung.* The lungs are frequently involved, the lesions being small and distributed symmetrically, especially in the middle and lower parts. Sometimes there appears to be a diffuse fibrosis with somewhat dense shadows radiating from the hilum to the periphery. Sarcoidosis of the bronchial mucous membrane was present in a case reported by Bernstein and co-workers; this patient developed a bilateral hydrothorax. It is stated that the pulmonary changes may vary with the sarcoid condition of the skin; concomitant improvement in the two conditions has been noted. Secondary infiltration of the lungs may occur from sarcoidosis of the mediastinal lymph nodes, and this appears to be a common type. The more fibrotic lesions are probably older than the other varieties; in some cases resorption occurs with considerable clearing of the lung. Longcope and Pierson record the complete disappearance of hilar and parenchymatous lesions during the periods of six and 10 years. Polycythaemia has been described in association with pulmonary sarcoidosis.

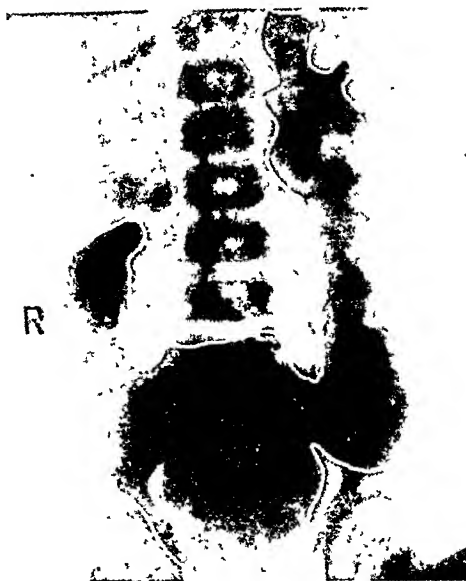


Fig. 19.

### Meningocoeles

There were six cases all with gross infection of the urinary tract. There are two types:—

- (a) The small systolic bladder dribbling all the time.
- (b) Retention with overflow.

*Type (a).* I believe that the small systolic type is the product of gross cystourethritis. Two cases treated in hospital by regular manual expression of the one to two ounce residual, and chemotherapy, have gained some measure of control and the bladders have become more tolerant.

*CASE No. 5. A girl aged five.* After being wet all her life and badly ulcerated she is now dry all day on two-hourly manual expression and her skin is healthy.

*Type (b).* The overflow type requires surgical treatment as early as possible. Two cases whose meningocoeles had been removed in infancy, and in whom manual expression was impossible owing to the tightness of the bladder outlet, were subjected to double lumbar ganglionectomy. After the first side was done there was no change; but immediately after the second ganglionectomy manual expression became easy and effective. Residual urine was reduced to two to three ounces, and in one case of a girl whose urine had been thick and ropy, the urine actually became sterile. Fig. 21 is a cystogram of this patient showing vesicorenal reflux. Both children relapsed six months after sympathectomies and subsequently a V-wedge resection of the bladder neck was performed on the first child

*Symptomatology.* It is an impressive feature of the disease that no symptoms or signs may be manifested in spite of extensive involvement of the lungs; this is an important fact when the diagnosis is being considered. The outstanding symptom is dyspnoea which may be related to pulmonary or cardiac dysfunction. The pericardium and myocardium may also be extensively involved by sarcoidosis. Cough, with or without sputum, is sometimes present. The only physical sign may be the presence of râles at the bases. Bronchopneumonia may occur as a result of secondary infection. These patients also appear to be susceptible to infection by the tubercle bacillus, and in a number of fatal cases death has been hastened by this infection in the lungs or other organs.

*Radiological Appearances.* There are fairly dense, linear striations representing infiltration of the lungs, chiefly in the lower half, and extending from the hilum towards the periphery (Fig. 6). In addition, there are areas of opacity varying in size up to 1 cm. in diameter (Fig. 7). There is no calcification present. When the mediastinal lymph nodes are enlarged representative shadows are present (Fig. 8). It is pointed out that the radiological appearances are not typical and in the differential diagnosis the following conditions must be considered: tuberculosis, carcinoma of the lung, especially miliary carcinomatosis, diffuse fibrosis, either non-specific or post-tuberculous, and pulmonary congestion (Fig. 9). Pneumoconiosis resembles sarcoidosis fairly closely, but in the former condition the nodules are more numerous and definite and linear striations are not so marked (Fig. 10). It may be difficult to differentiate between sarcoidosis and bronchiectasis, although in the former condition there is not the same tendency to cavitation and the lesion is more diffuse.

*The Lymph Nodes.* These are involved in the majority of all patients with sarcoidosis and sometimes the enlargement is very marked. There may be generalised enlargement, or a certain group may be involved such as the axillary, submental, submaxillary, epitrochlear, inguinal, femoral or mediastinal. The latter group is frequently involved. Sarcoid-like lesions have been described by Nickerson in association with other affections including lymphadenoma, and in the aortic lymph nodes of a patient who died of cancer of the stomach. Jaundice was present in two cases reported by Goeckerman, which may have been due to enlarged lymph nodes in the hilum of the liver causing pressure on the biliary ducts. In another group of cases there is involvement of the mediastinal and bronchial lymph nodes with infiltration of the lungs. In certain cases there is an intense and extensive œdema of the lymph nodes.

The lymph nodes are discrete, mobile, painless and they may retrogress in size. If a thorough search is made for tubercle bacilli in sections stained by the Ziehl-Neelsen technique, they are sometimes found. I am indebted to Dr. R. A. Willis for the following case-records illustrating this point:

*Case No. 4.*—Female aged 10 had enlarged lymph nodes in the neck and axilla for over two years. A lymph node was excised; it measured nearly 2 cm. in diameter and consisted of moderately fibrosed lymphoid tissue

investigated very early on, and the associated urinary pathology is more serious to life than is the sensory or motor loss in the limb.

Manual expression of the bladder, hourly at first and then two-hourly by day, should be done by the mother. Constant chemotherapy helps to lessen the infection. Those with retention overflow may require a

## UROPATHOLOGY IN FUNCTIONAL GROUP

### TOTAL CASES

186

STAGE I	17	
II	9	
III	5	
IV	4	
VII	6	
DAY WETTERS	1	
	<hr/>	
TOTAL	42	22%
INCLUDING THREADWORMS	54	29%

Fig. 25.

wedge resection, and as they grow they learn to empty the bladder by raising their abdominal pressure. Enough tone persists at the outlet to prevent leakage.

If there is incontinence without retention, or if the retention has been relieved and the incontinence persists, a modification of Lowsley's (1936) operation to reduce the lumen of the bulbous urethra is suitable for boys, and has met with some success.

## PROGRESS, PROGNOSIS AND TREATMENT OF ENURESIS

It has not been possible to follow up large numbers over a long period of time, and, therefore, I have taken three months as being a fair period to give even the surgeon a chance. Progress can be assessed by the movement of the symptoms to a more mature symptom group (Fig. 26). For instance, from Stage I, 30 cases had moved into Stage III. They had lost their day symptoms and had started to have night remissions. This represents a major development and many of these children actually moved up to Stage III within a week of their first visit. Progress in Stage II has been just as good. Here 35 out of 52 cases showed very marked improvement. Progress in Stage III is also good but the disappointing part is that Stage I and II cases, having moved up to Stage III, seem to stick there.



Fig. 6. Radiological appearances in sarcoidosis of the lung. Fairly dense linear striations representing infiltration of the lung can be seen chiefly involving the lower half and extending from the hilum towards the periphery.

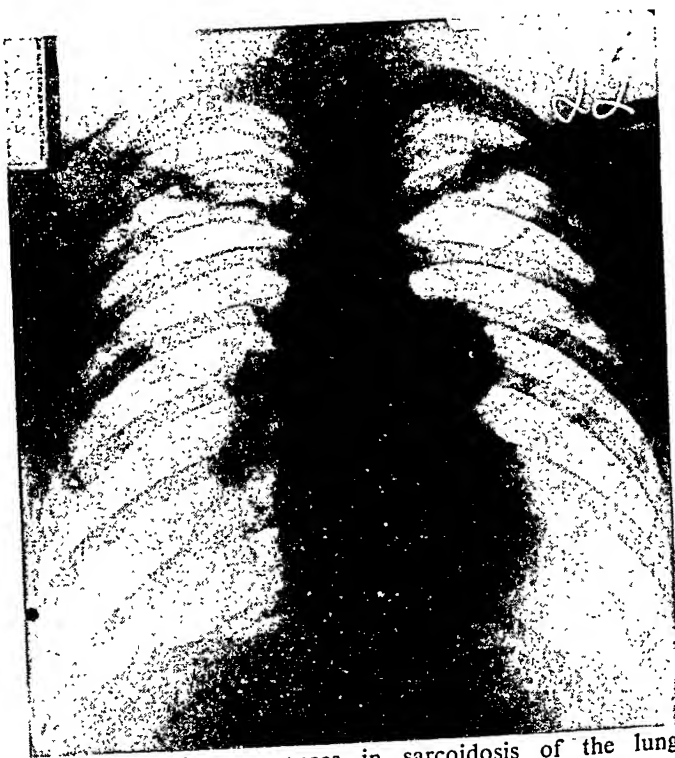


Fig. 7. Radiological appearances in sarcoidosis of the lung. In addition to linear striations areas of opacity are seen.

taking place. Ephedrine, on the other hand, may work in one of three ways. It may antagonise the detrusor irritability which is parasympathetic. It may enhance the tone of the bladder neck—and here I do not agree with those physiologists who insist that the parasympathetic plays no part in the tone of the bladder neck. It does.

For over a year I have been using Methyl-Ephedrine (in doses of  $\frac{2}{3}$  gr. for children from four-seven years twice a day) and this is certainly much more effective and prolonged in its action than Ephedrine itself and free from side effects. Fig. 29 shows a change brought about by drugs.

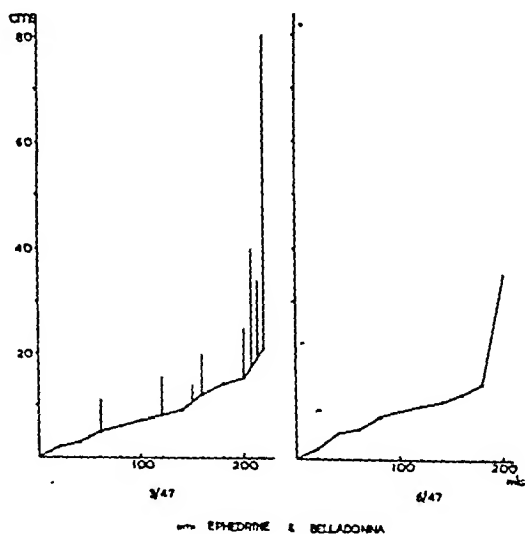


Fig. 29.

Phenobarbitone may help the child who is nervous and excited, but on the whole its use tends to make the enuresis worse.

Drugs used to lighten sleep are of the Ephedrine or Ephedrine derivative type, Amphetamine and Dexedrine. Dexedrine is the best, and is very effective in some of the heavy sleepers. A dose of 2.5 mgms. at night for a child of seven is appropriate.

In certain cases there is no doubt that sexual excitement shown in boys by priapism is a factor. It occurs early in the night or as sleep begins to lighten in the morning when the bladder is full. For this reason it is worth trying some cases on small doses of phenobarbitone or bromide at tea-time and it is not taken as defeat to have to try a series of drugs in the hope that one will work. Sooner or later one will be rewarded. "Try it and see" was one of Hunter's great *dicta*. Stilboestrol has been tried on some of the boys and it does seem to be effective in reducing the priapism (0.5 mgms. at night for 10 nights for a boy of 10) and in a



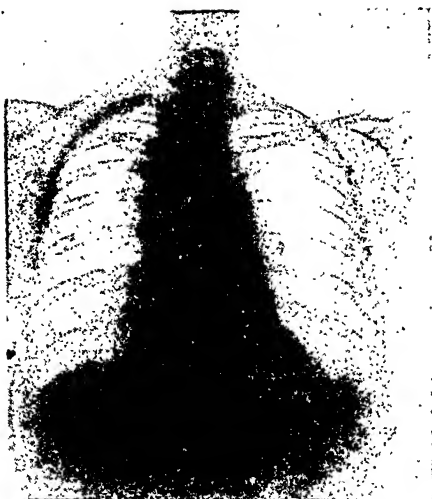


Fig. 8. Radiological appearances in sarcoidosis of the lung. Large shadows representing enlarged mediastinal lymph nodes are seen.



Fig. 9. Radiological appearances in sarcoidosis of the lung showing diffuse infiltration type of the disease resembling miliary carcinomatosis.



Fig. 10. Tomographic appearances in sarcoidosis of the lung.

## THE LIBRARY

Two further letters of John Hunter and notes on Rockingham's last illness from Hunter's Case Book.

THROUGH THE KINDNESS OF the Marquis of Lansdowne it is possible to publish two letters written by John Hunter which are preserved in the Muniment Room at Bowood. The first letter gives a glimpse into the human side of Hunter's character. At the time it was written he was Surgeon-Extraordinary to the King and at the height of his career. Though handicapped by ill-health he was busy at St. George's Hospital and with the cares of a large practice ; added to this he was working half through the night at the elucidation of ideas which, as he said, filled his head "like a bee-hive." Yet in the midst of this turmoil we find him quietly sitting down to write a letter on behalf of a humble patient who needed the help that he himself could not give. The fact that the man was a butcher who "often brought me curious parts of animals" doubtless quickened his interest and set him to do his best for the patient. We do not know that his efforts bore fruit, although a passage in the second letter implies that My Lord's interest was aroused, but to Hunter's credit the attempt was made and it proves his readiness to help a friend.

The letters, of which copies have been presented to the Library, were addressed to the first Lord Lansdowne and are as follows :—

MY LORD,

I have several times of late made Barkley square in my way, with an intention to wait upon your Lordship ; but as it was to ask a favour, my Heart as often faild me. (altho I do not think myself a Coward, nor your Lordships manner austere) but being consciouse of the many teasing applications, that both your Lordships known natural disposition to assist, and the expectations that your situation raises, in those who have the honour of knowing you, were the causes of that delicacy, which your Lordship has reason to wish was more universal ; but as I could not well refuse a promise to apply to you I now take the liberty to fulfill that promise. There is a poor man who is a Butcher by trade, but so unhealthy in London, that he cannot follow his business. He has often brought me curious parts of animals, and has a turn of mind with a degree of ingenuity that far exceeds many in better situations. He wants a Tide waiter's\* place. I spoke to Sir William Musgrave about him, who promised to put him down as an occasional one, but that imploy is so uncertain, that it will be of little use. I spoke to Mr. Bromfield to speak to the Marquise of Rockingham, and I was in hopes (when I was call'd to him) to have been able to have done it myself. If your Lordship would chuse to see me, I will call to know when. I have the Honour to be with great Respect your Lordships most Humble servant.

JOHN HUNTER.

Jermyn Street.

July 29th, 1782.

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\* *Tide-Waiter*.—An officer who awaits the arrival of vessels to secure the payment of duties.

with many well-defined follicles of large pale cells scattered throughout the section. These follicles were identical with the epithelioid cells of tubercles, accompanied by lymphocytes and plasma cells. There was no caseation and a small number of giant cells were present. The initial diagnosis was "reticulosis." A thorough search of Ziehl-Neelsen stained sections disclosed undoubted tubercle bacilli.

*Case No. 5.*—Female aged 13 suffered from vague abdominal pain for which appendectomy was performed. Six months later enlarged lymph nodes in the groin and epitrochlear regions developed with evening pyrexia and leucocytosis up to 18,000 per cmm. An X-ray of the chest showed no abnormality; the Wassermann reaction was negative. Two months later iridocyclitis developed and the axillary lymph nodes became enlarged. The Mantoux and von Pirquet tests were negative, both human and bovine. An epitrochlear lymph node was excised for microscopical study, and this showed a similar structure to the node in Case No. 4, with many more giant cells. No tubercle bacilli were found in the sections. The difference between sarcoidosis and tuberculosis could not be determined.

*Case No. 6.*—Male, aged 14, with generalised enlargement of lymph nodes and some small nodular skin lesions. An inguinal lymph node was excised and the diagnosis of sarcoidosis made. Further sections were examined for tubercle bacilli which were eventually found.

The importance of differentiating the enlarged lymph nodes of sarcoidosis from other causes of lymphadenopathy is obvious and is important from the surgical standpoint. In doubtful cases additional evidence may be provided by radiological examination of the chest and the bones of the hands and feet. Finally, it may be essential to excise an accessible lymph node for microscopic study.

*The Bone Lesion.*—It appears that osseous lesions are found in approximately 20 per cent. of patients suffering from sarcoidosis. These lesions tend to be progressive, but if the disease is arrested the appearance of the bones may become almost normal again. In other cases, however, there is considerable permanent loss of bone tissue. The bones of the hand (Fig. 11) and foot are usually affected; the long bones of the extremities are rarely involved, but there are descriptions in the literature of changes in the lower ends of the radius and ulna, around the elbow joint and in the body of a vertebra.

On examination the digits are irregularly enlarged, the tips become squared with some dorsiflexion at the distal interphalangeal joint. In some cases subcutaneous nodules appear symmetrically around the interphalangeal joints. When the disease is advanced a picture *simulating* leprosy is produced, with painless mutilation of the fingers and the gradual disappearance of the terminal phalanges. Cases have been described with involvement of the metacarpal and carpal bones, especially the scaphoid. Radiological examination shows various appearances; initially there is thickening of the trabeculae in the end of a phalanx, followed by the development of small punched-out areas forming cystic



Fig. 1. KING JAMES IV (1473-1513)  
(Reproduced by kind permission of the Hon. Mrs. Sterling of Keir.)



Fig. 11. Radiological appearances of hands in sarcoidosis showing the typical cystic spaces.

spaces which vary in size from pin-point to 1 cm. diameter. The trabeculae in the inter-cystic areas become dense and sclerotic. In some cases the whole phalanx is affected. There is no accompanying periostitis and the interphalangeal joints are not involved. The cortex is rarely broken and the bone may show a small degree of uniform enlargement. There may be signs of inflammation, but no sinuses are formed in the overlying skin. These bone changes may be present in sarcoidosis without the presence of skin lesions.

Jungling described the histological picture as that of non-caseating tuberculosis the lesion consisting chiefly of epithelioid cells, a few giant cells, and necrosis is absent. Tubercle bacilli have been demonstrated in these lesions on rare occasions.

The condition must be differentiated from the following lesions :

*Tuberculous Dactylitis.*—This is seen usually in children, and periostitis with bone atrophy is marked. The presence of discharging sinuses and sequestra is common.

down with "Sik a dad" (such violence) and to those who ran to his help he said that he had broken his thigh bone and he hoped never to "gang again" (repeat the trial). As the ancient chroniclers say, "Al war like to cleine (split) of lauchter." His misfortune he attributed to the fact that in his wings there were some hens' feathers which yearned for and coveted more the midden (dung hill), than the sky.

### The King as a Pediatrician

During his reign what we would now call Siamese twins were born, viable and healthy, with separate bodies but united with their lower limbs in common. These he had carefully brought up and trained in music, so that they could sing duets, one the treble, the other the tenor. They also were fluent linguists.

### The King as a Linguist

The King, being intrigued to find the fundamental language of the human species, had two new born infants marooned and carefully attended to on Inchkeith Island by a mute nurse. The answer is not available; some said it was Hebrew.

### The King as an Educationist and Jurist

He enacted through his Parliament a law compelling all noblemen to send their eldest sons to be educated "until they be competently founded and have perfect Latin and understanding the Laws, so that they might administer better justice on behalf of the King."

In 1505, the University of old Aberdeen was completed and named Kings College. It, although younger than St. Andrews and Glasgow Universities, was the first British University to give instruction in medicine.

### The King as an Operating Surgeon

For a full account of the many occasions on which payments are noted in the Lord High Treasurer's accounts as being made to leeches and apothecaries, I would refer you to a most attractive article by Douglas Guthrie in XXI, Vol. 2, The Bulletin of the History of Medicine. The King's personal services as an operating surgeon he gave not only gratuitously, but in addition he paid the patients.

For the blood letting of Dominico in 1491, he paid 28 shillings; for the extraction of one tooth, 14 shillings.

In 1504, at the cost of two shillings, he healed John Balfour's "sair leg."

On the 1st July, 1505, the Barbers and Surgeons appeared before the Lord Provost, Baillies and Councillors of Edinburgh, then sitting in session in the Tolbooth of the said City, and presented a petition and sought to be awarded a Seal of Cause and Charter of Privileges. They claimed that "it was well known to their wisdoms that they upheld an

*Syphilis of bone.*—This disease, especially the congenital type, sometimes affects the phalanges but the lesion is more frequent in the diaphysis than in the head. The cortex of the bone is thickened and some degree of periostitis is present.

*Osteitis Fibrosa Cystica.*—This disease is seldom confined to the phalanges but it is more generalised in nature and progressive. Pathological fracture is more likely.

*Chondromatosis.*—The deformity of the hand is much more serious with greater enlargement of the bones and definite tumours are present.

*Gastro-Intestinal Sarcoidosis.*—This variety of the disease is of interest and importance to the surgeon and, since it is now recognised, more cases will doubtless be reported in future.

*Stomach.*—An interesting case is described by Gore and McCarthy and is the only one to my knowledge in the literature. The patient was a male, aged 26, and a pre-operative diagnosis of peptic ulcer, gastric syphilis or gastric neoplasm was made. At operation a gastric resection was carried out. The specimen removed showed a crescentic, moderately deep ulcer 5 cm. long and 1-2 cm. in width straddling the greater curvature 8 cm. proximal to the pylorus. Proximal to the ulcer the mucosal folds were thickened and formed a sharp overhanging wall. There was a tendency for puckering of the folds in the direction of the ulcer. The distal margin of the ulcer was poorly defined. The stomach wall showed marked scarring and thickening of the submucosal layer underlying the ulcer and extending towards the pylorus. The muscularis layer was intact and hyperplastic. Histological examination showed the following appearances: the ulceration barely penetrated the muscularis mucosæ. The bed consisted of a thin layer of chronically inflamed granulation tissue, the underlying submucosa was œdematous and moderately scarred. The submucosal vessels showed endarteritic changes and heavy mantles of round and plasma cells accompanied the vessels. In the mucosa and superficial submucosa adjacent to the ulcer, there were nodular aggregates of epithelioid cells, but there was no caseation or necrosis and giant cells were rare. The muscularis was thickened by scar tissue and round cell infiltration. The serosal surface contained a number of small lymphoid nodules (in the centre of which epithelioid cells and an occasional Langhan's type giant cell were found); concentric laminated basophilic giant cell inclusions were also demonstrable. A regional lymph node showed similar nodular clusters of epithelioid cells.

It is impossible to form an opinion concerning the correct treatment of gastric sarcoidosis with the experience of one case; doubtless spontaneous resolution might occur, but, on the other hand, secondary complications may arise which render surgical interference advisable. Furthermore, resection and histological study will often be necessary in order to determine the diagnosis.

*Small Intestine.*—There has been some discussion regarding sarcoidosis of the small intestine and several cases have been described in association

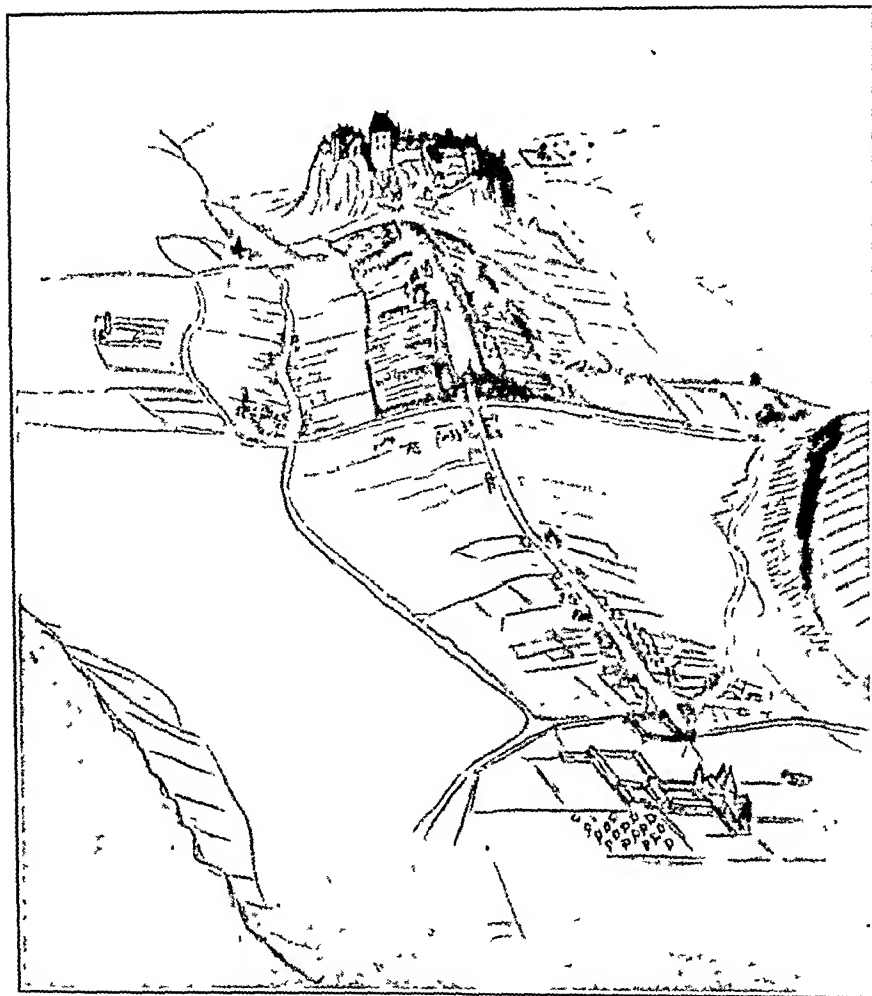


Fig. 2. Reconstructed view of Edinburgh, *circa* 1450, showing the Royal Mile leading from the Castle to Holyrood Palace and Abbey. Beneath the Castle is the Walled City of Edinburgh with its high buildings down which runs the High Street with St. Giles Cathedral and the Tolbooth on the left. At the Netherbow it joins the Canongate. On the right is the Nor' Loch : on the left the smaller, South Loch. Adjacent to it is Greyfriars, and leading from it is the Canongate with the Kirk of Field on the left, and beyond Blackfriars where subsequently the Surgeons' Hall and Surgeons' Square were built.

(From Edinburgh 1329-1929, Commemorative Volume 1929.)

The awarding of the Seal of Cause and Charter of Privileges to the Barbers and Surgeons by the Lord Provost and Council of the City of Edinburgh was not an isolated incident. On the contrary it was the culmination of a policy and scheme of municipal and national government, some fragments of which still remain.



with systemic sarcoidosis. Isolated sarcoidosis of the small bowel is uncommon and therefore two cases reported by Wagensteen and co-workers are of great interest.

*Case No. 7.*—Female, aged 21, had experienced lassitude, weakness and anorexia for one year followed by diarrhoea and fever for eight months. Physical examination was negative. Radiological examination of the small intestine showed a diffuse change in the mucosa which was swollen and irregular with dilatation of local loops and stasis. These changes were diffuse and suggested extensive polyposis, differing from regional ileitis or ileo-jejunitis. Radiological examination of the chest and hands revealed no abnormality. The Mantoux test was negative. Resection of the involved bowel resulted in a remission of five months, after which there was a recurrence of mild fever and diarrhoea. A second operation was performed when 75 cm. of the small intestine, including all the ileum, was excised. The patient regained excellent health, but mild fever persisted with some anæmia and an increased sedimentation rate, indicative of activity in the remaining portion of bowel or viscera.

Examination of the specimen showed extensive nodular involvement of the resected loops of bowel. The mucosa presented a hobnail appearance and there was diffuse involvement of the mesenteric lymph nodes. The microscopical appearances were those of sarcoidosis, with epithelioid tubercles with and without giant cells; caseation was absent.

*Case No. 8.*—Female, aged 25, had experienced weakness, nausea, vomiting, diarrhoea, abdominal distension and progressive loss of weight for two years. Examination showed clubbing of the fingers and fever, 99°-101°F., but was otherwise negative. The Mantoux test was negative. Radiological examination of the small intestine showed the appearances of regional ileitis with changes in the jejunum of undetermined type. There was marked hypermobility and stasis in several adherent segments of the bowel. Several areas suggestive of polyposis were also seen. At operation resection of the involved ileum and some of the cæcum was performed. This was followed by immediate improvement which has been maintained. The fever subsided, 25 lb. were gained in weight, but there was persistent mild diarrhoea.

#### RELATIONSHIP BETWEEN INTESTINAL SARCOIDOSIS AND REGIONAL ILEITIS

The symptomatology of these two patients simulated that of regional ileitis in certain respects, but some of the characteristics of the latter disease were absent, including a swelling in the right iliac fossa, local peritonitis or fistula formation. The radiological appearances were generalised rather than localised and the polyposis appearance is not seen in regional ileitis.

There has been some controversy over this problem. Snapper rejects the conception that the two conditions are related, and Wagensteen and co-workers differentiate between them. In the cases of proved sarcoidosis

In their petition they state—"We believe it is well known to all your wisdoms that we uphold an Altar situated within your College Kirk of Sanct Geill in the honour of God and Sanct Mongow our patron." The inference naturally follows that the surgeons and barbers, previous to their application, had been joint supporters of this altar. The late Mr. Creswell, when officer to the college, discovered among the college muniments a document conveying the right to the Altar, not upon the barbers and surgeons, but upon the Kirk Master and Brethren of the Barber Craft only. This document, a certified record of the Burgh Records, is dated 24th April, 1504. Thus, while it confirms the existence of the Barbers as a Society before their coalition with the surgeons, there is nothing to indicate that they had any official connexion until the joint application, a conjunction probably due to the surgeons, then few in number, not having a chapel of their own.

Naturally from the number of crafts it was impossible for each to have a separate chapel, thus certain joint applications were made—the Barbers and Surgeons, the Masons and Wrights, and the Hammermen who comprised Blacksmiths, Goldsmiths, Lorymeris (clockmakers), Sadlers, Cutlars, Buclar makers (shield makers), Armourers and others. Although making joint application, it is clearly brought out that each must strictly confine his services to his own job, a point of importance that has to be considered in the case of the Barber and Surgeon, and in its day led to much confusion.

In the Lord High Treasurer's accounts for 1527 it is recorded by an act of Parliament that "our Sovereign Lord granted a yearly fee and pension to his servant George Leithe his surgeon for the days of his life." He was then Deacon of the Barber Surgeons. In 1542 he, with four other surgeons, received twelve pounds for passing to the Borders for the curing of all men who happened to be hurt by the Englishmen. On the threat of one of the recurring invasions in 1530 the Craft mobilized 27 of their members for a defence force. One of their number was Gilbert Primrose, an ancestor of Lord Rosebery. He was one of the most prominent of the early barber surgeons and was thrice elected deacon and acted as Surgeon to King James the Sixth and First. He did much for the welfare of the craft and was responsible for raising the entrance fee to 60 pounds for a surgeon and 40 pounds for a barber; the latter was also required to certify in the City records that he would not use any of the practices of surgery under a penalty of 20 pounds. The apprentice fee was raised from 20 shillings to 40 shillings. The weekly penny formerly given to the Altar was changed to a levy of six shillings and eightpence a quarter towards a pension fund for persons of the Craft "that might happen to decay."

In 1909 the Royal College of Surgeons commemorated the opening of the new hall, and the late Lord Rosebery, the direct descendant of Gilbert Primrose, attended and brought with him a remarkable trophy.

of the small and large intestines the disease pattern of regional ileitis was absent. For example, in a case of sarcoid of the ascending colon, there was no involvement of the terminal ileum which is so common in regional ileitis. Williams and Nickerson carried out an interesting experiment by taking an extract from a skin lesion of a typical case of cutaneous sarcoidosis and injected it intradermally into four other cases of sarcoidosis. A red papule developed within 36 hours in all instances, while no reaction occurred in four controls who exhibited no evidence of sarcoidosis. Two cases amongst the four positive reactions exhibited thickening of the small bowel with lesions interpreted as sarcoid, and both had been diagnosed as regional ileitis. In the opinion of Homans and Hass, the giant cell reaction and the formation of tubercle-like lesions is the response to a foreign body which in the majority of instances, in all probability, is a lupoid. There is a general tendency in the literature to accept this view.

Hadfield made a study of 20 cases of regional ileitis and described the histological changes in the terminal ileum and its related lymph nodes. The average length of ileum involved was 19 cm., with variations from 4 to 60 cm. The terminal ileum and ileo-cæcal region were involved in 17 cases; the distal ileum in three cases. A fistula between the lumen of the bowel and the abdominal wall or urinary bladder developed in seven cases. The condition was not found in the jejunum or the colon, apart from co-existing involvement of the small intestine. The outstanding features macroscopically were the marked thickening of the wall of the ileum, especially in the submucous layer, and the presence of ulceration in all cases. Ulceration may be superficial, of slight or moderate degrees, or deep with marked sloughing, cicatrization, stenosis, the formation of intramural abscesses and the development of multiple fistulæ.

Discussing the ætiology of regional ileitis, Hadfield considers that the giant cell systems in the bowel and lymph nodes are indistinguishable from those of tuberculosis, but their tendency to retrogress without excessive scarring, the absence of caseation and acid-fast bacilli cause doubt concerning their tuberculous origin. He states that, in spite of these facts, tuberculosis cannot be dismissed as an ætiological factor until it has been excluded by careful cultivation and inoculation of material from a large series of cases. There is sufficient evidence against the disease being a complication of active pulmonary tuberculosis. Hadfield calls attention to the similarity between regional ileitis and sarcoidosis on histological grounds. There is the same tendency to slow spontaneous retrogression and healing; and a specific infective agent has not been isolated in either condition. It is important to ascertain the condition of patients with regional ileitis after a period of 10 years and see whether there is evidence of generalized disease present such as is found in sarcoidosis. The history of regional ileitis is much shorter, and after five years the primary lesion has retrogressed, or is obliterated, and the picture is dominated by complications such as ulceration and its sequelæ.

be admitted in time coming except he be tried and found qualified in surgery." In consequence of this, the simple barber soon became practically extinct.

Some 10 years later, the apothecaries were affiliated to the surgeons, so that the craft now contained surgeons, surgeon barbers, surgeon apothecaries and the remnants of the simple barbers.

During the 34 years following the passage of this act, only one single surgeon barber was licensed, which resulted in the Town Council reminding the surgeons of the obligations incurred when they were granted a monopoly; and thus, at the magistrates' instigation, they at once licensed a number of simple barbers, with the result that in 36 years' time, 99 were practising within the city and each of these had paid an entrance fee of 500 merks (£28 2s. 6d. sterling, Victorian). At the same time they were given no privileges in the Surgeons' Corporation.

The usual consequence resulted—an action before the High Court of Session, during which it came out in evidence that since 1682 they had contributed 140,000 merks. The decision of their Lordships was a complete division of the crafts, by means of which the barbers lost caste and the surgeons money. Deprived of their handsome revenue the surgeons were plunged into financial difficulties. Their hall they turned into dwelling houses, retaining but a single room. Their herb garden and land they feued and from it the famous Surgeon's Square arose—the old Surgeon's Square where was born the Medical Faculty of Edinburgh University.

The concluding paragraph of that most charming Thomas Vicary Lecture by Sir D'Arcy Power reveals most graphically the consequences of a similar separation of the barber, the practical business man and the financially simple-minded surgeon, revealing thereby the value of a union, which to some seemed incongruous and, to the generation that thought of such things, derogatory to their dignity.

The Seal of Cause and Charter of Privileges granted to the Barber Surgeons of Edinburgh in 1505 and confirmed by Royal Charter by James the Fourth in 1506, laid down the duty of this Corporation, in common with other crafts, to bear witness to the religious faith they testified. Soon thereafter, a storm arose and "the flash of that satiric rage, which, bursting on the early stage, branded the vices of the age, and broke the Keys of Rome." The Aisles and Cloisters, where the devout might commune with their Maker, were cast down, cold reason was enthroned and a religious hierarchy, with the great John Knox as its Kirkmaster, established.

Those of us who, like myself, were born and brought up in the faith he professed, while testifying to the services he rendered his country, at the same time never could forgive him for his hostility and rudeness to that devout, courageous lady, Mary Queen of Scots. We shall, however,

Thus, while there is much evidence against the view that regional ileitis and sarcoidosis is a disease entity, the relationship cannot be completely disrupted until a series of cases with regional ileitis has been observed for a period of 10 years.

*Colon.*—I have been unable to find a description of sarcoidosis of the colon in the literature, so that the report of a case under my care is of interest.

*Case No. 9.*—Male, aged 53, a railway porter, was admitted to hospital complaining of epigastric pain occurring half an hour after food.

*History.*—The pain commenced a year ago and was occasional at first, but later experienced daily and lasting up to 4 hours. Sometimes it was present for a period of 24 hours. It was relieved by vomiting which was a frequent occurrence. For 5 months there was irregularity of bowel action with intermittent attacks of diarrhoea. Anorexia was present. Loss of weight—three stones during 8 months. Past history and family history—nothing of significance.

*Examination.*—Patient has lost weight; tongue clean; neck—no enlarged lymph nodes; chest—no gross abnormality. Abdomen: there is fullness in the right iliac fossa with tenderness; the cæcum is distended and there is a lump in the region of the ascending colon. Liver is just palpable; kidneys and spleen are not palpable. Rectal examination is negative.

*Investigations.*—Gastro-intestinal radiology—barium meal showed no abnormality in the œsophagus, stomach or duodenum; barium enema showed a considerable stricture in the ascending colon, the appearances indicate a neoplasm. Chest—X-ray showed no abnormality. Hands and feet—X-ray: there is a large cyst in the left scaphoid; osteo-arthritis changes in feet (Fig. 12). Blood picture—R.B.C. 4,900,000 per cmm.; Hb. 85 per cent., W.B.C. 20,200 per cmm.—polymorphs. 67 per cent.; plasma proteins and chlorides within normal limits; Wassermann and Kahn reactions are negative; plasma ascorbic acid 1.3 mg. per cent. Urine—no abnormality.

*Operation.*—Right hemicolectomy with an ileo-transverse colostomy. Uninterrupted recovery.

Specimen removed consisted of the terminal portion of the ileum, cæcum, appendix, ascending colon and proximal portion of the transverse colon. The walls of the bowel are thickened with the exception of the ileum. There is marked fibrotic lesion causing considerable stenosis of the ascending colon. Microscopy showed the histological appearances of sarcoidosis (Fig. 13). Multiple characteristic foci comprising groups of reticulo-endothelial cells are present in the submucous and muscular coats of the bowel wall, together with occasional similar foci in the serous coat. The majority of these are associated with multinucleated giant cells somewhat resembling those of tuberculosis. On the other hand, several of the giant cells contain centrally placed nuclei and there is no evidence of caseation. Two lymph nodes showed characteristic lesions of sarcoidosis

# CHEMOTHERAPEUTIC DRUGS : A REVIEW

Lecture delivered at the Royal College of Surgeons of England

on

8th December, 1948

by

George Brownlee, B.Sc. (Glasg.), Ph.D. (Lond.)

Wellcome Research Laboratories, Beckenham, Kent

## History and Definition

THE WORD CHEMOTHERAPY was fathered by Paul Ehrlich, who used it in a number of ways, but always with the idea of specificity. The concept of specific chemical therapy is seen in Ehrlich's (1890) attempts to exploit the affinity of methylene blue for nervous tissue in the treatment of neuralgia, since only those substances "eaten" by the cell could be expected to influence it. Ehrlich returned to his view of distribution of an active unaltered chemical substance (1907) which he described as "biological therapy" and again in 1913 (Ehrlich, 1913) advanced the principle of "no action without fixation," as an essential for successful chemotherapy. These principles he described as chemotherapy, and were summarized as *distribution* to the site of action, *fixation* by the affected cells, and *specific drug action* by the chemical. In 1907 we find Ehrlich describing "specific chemotherapy" as the treatment of infections by administered chemical compounds, with the object of irreversibly deranging the parasite cells so that they died without unduly harming the host. It was the subsequent success which attended the development of these ideas which has made the term come to mean, mainly, *specific antimicrobial chemotherapy*.

To-day authorities differ in their definitions of chemotherapy. Some have included the treatment of cancer with therapeutic agents, some the use of antitoxins and antibacterial immune bodies; some include the use of locally applied drugs, and there are others who would include all chemical drugs, wherever their ultimate site of action.

Preoccupation with the precise definition of the word "chemotherapy" is of recent growth, and we must look to the contributions which specific antimicrobial chemotherapy has made to the fundamental studies of drug distribution in tissue and excretion and to the understanding of the mode of action of drugs in general, to appreciate the underlying causes.

It would be unprofitable to succumb to a tyranny of words which demands precision where there is none; rather let it be recognized that the inconsistency of terminology reflects the current fluid condition of unformed ideas. Meanwhile for our purposes it is necessary to define the subject under discussion here as "specific antimicrobial chemotherapeutic drugs."

## ANTIMALARIAL DRUGS

The occupation of Java by the Japanese in 1942 deprived the Allies of 90 per cent. of the available cinchona production and seriously

distributed mainly in the subcapsular sinuses, but also to some extent in the medullary sinuses. Several of these foci showed evidence of becoming confluent.

The surgical implications of this type of lesion are important. The symptomatology and radiological appearances of the colon were in favour of a carcinoma which was the pre-operative diagnosis. At operation it was thought that the lesion was a fibro-carcinoma of the colon and a radical excision was performed. Reviewing the case it is felt that this was the correct operative procedure for a constricting sarcoid of the ascending colon. It is of interest to notice that the terminal ileum was normal, a point of distinction from regional ileitis.

*The Spleen.*—Splenomegaly is commonly present in cases of sarcoidosis and the degree of enlargement may be considerable. In an interesting series of cases examined at autopsy by Nickerson the most constant feature was unexplained splenomegaly with or without abdominal lymphadenopathy. In 4 cases the spleens weighed 200, 230, 640 and 890 gm. respectively. The external surfaces were smooth and glistening. In the largest spleens there was increased resistance on section which revealed pale pinkish grey surfaces, firm and dry, and almost completely replaced by large numbers of pale grey nodules from 1 to 3 mm. in diameter. The normal architecture was obscured. The smaller spleen

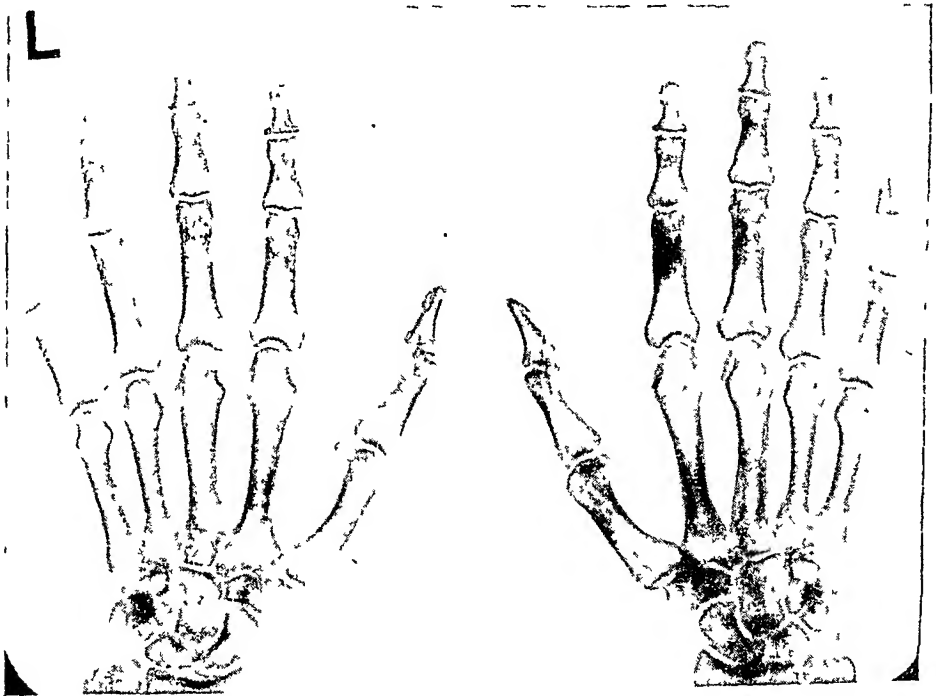


Fig. 12. Radiological appearances of hands of patient with a sarcoid of ascending colon showing a cyst in left scaphoid and early cystic changes in the phalanges.

tissue-phase schizonts of both parasites are insusceptible, but that the tissue-phase of only *P. falciparum* is of naturally short duration.

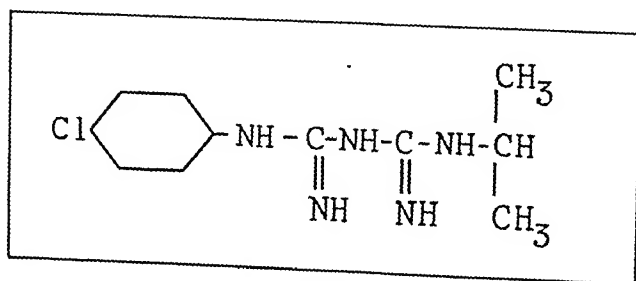
It had been observed by Sinton (1944) in India that a combined course of quinine and pamaquin was more effective in preventing relapses of benign tertian malaria than any other single drug. Kelleher and Thompson (1946) similarly found that of those treated with quinine and pamaquin only 10 per cent. relapsed, while 30 per cent. relapsed after mepacrine alone. This lead provided by pamaquin, formerly the German plasmochin, was actively followed in America. The most promising member of this group of substituted methoxyquinolines selected for study was pentaquine; it is less toxic to man than pamaquin and is the most active drug (equally with pamaquin) in bird malaria. For this compound it has been claimed that it reduced the expected relapses due to *P. vivax* from 96 per cent. to 16 per cent. in severe cases, and to 4 per cent. in moderate cases (Alving, 1947). A similar figure of 12 per cent. is quoted by Monk (1948).

### Chloroquine

A German preparation, sent to North Africa to be tried as an anti-malarial agent, was discovered when the Allied Forces occupied Tunis in 1943. This was sontoquin, made by I.G. Farbenindustrie. The lead proved by sontoquin, also known as resoquin, led to the discovery of the related substance, chloroquine. It proved more active than mepacrine, did not stain the skin yellow, and was found to suppress the relapses of benign tertian malaria if a dose was taken weekly. After large-scale trials chloroquine was accepted by the American Army authorities and would have replaced mepacrine in the field had hostilities continued. The chemical relation of the antimalarial drug is shown in Fig. 1.

### Paludrine

The researches which created paludrine were inaugurated by Imperial Chemical Industries in 1942. They were made possible by the development of a new chemotherapeutic test in chickens infected with *Plasmodium gallinaceum* (Curd, Davey and Rose, 1945). Briefly, six-day chicks were infected into the jugular vein with a large inoculum of parasitized red cells from a chick infection not older than five days. Infection was at its peak on the fifth day unless treated from the time of inoculation with a suitable suppressive, like mepacrine.





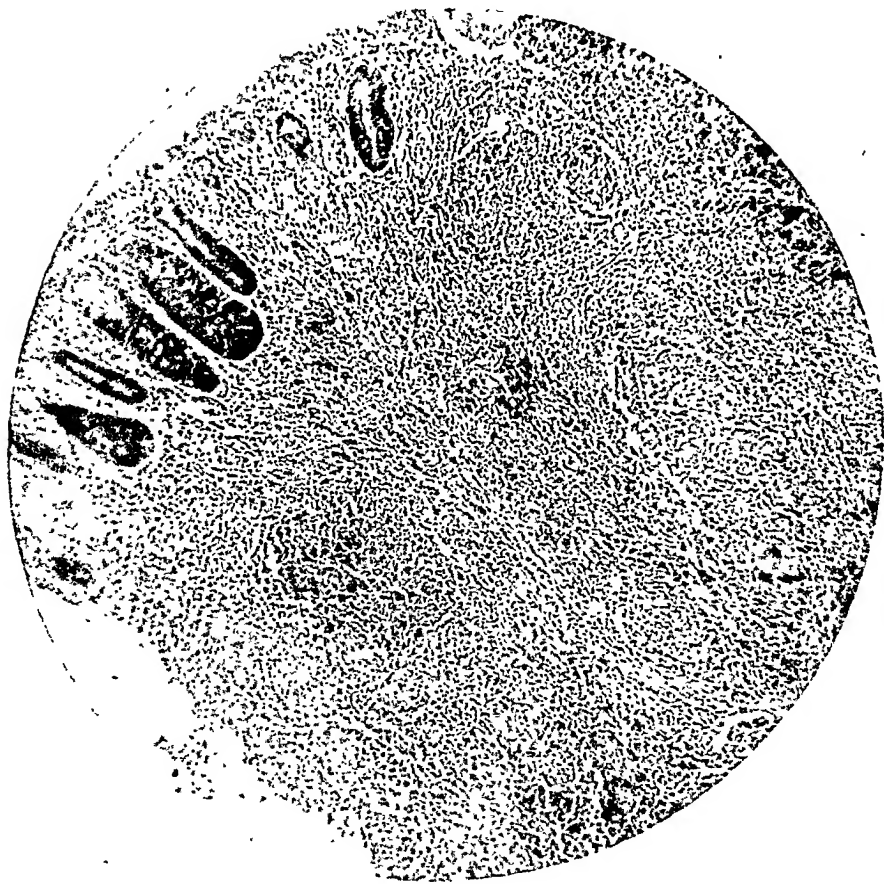


Fig. 13. Low-power photomicrograph of part of the mucosa of the ascending colon. The sub-epithelial zone is occupied by some hyperplastic lymphadenoid follicles. Towards the lower margin are some small sarcoid lesions associated with giant cells.

possessed normal resistance and moist reddish grey surfaces with scattered pale grey nodules. In four cases there was associated hepatomegaly, the largest one showing definite evidence of cirrhosis. When there is co-existing splenomegaly and hepatomegaly the condition must be differentiated from Banti's syndrome; in the literature several cases have been thus diagnosed and splenectomy performed. After operation the true nature of the disease was discovered. Dr. W. M. Firor, of the Johns Hopkins Hospital, wrote to me recently concerning such a case, stating that the splenectomy was fairly easy to perform and the patient was well 2 years ago.

Attention is called to the condition described as tuberculous splenomegaly and the view is put forward that certain of these cases may be described more correctly as sarcoidosis. It has been stated by Hoyle and Vaizey that the most frequent evidence of hæmatogenous dissemination of tuberculosis, elsewhere than in the lungs, is enlargement of the

against *P. cathemerium* and *P. relictum* in canaries and *P. lophurae* in ducks.

In man (Adams *et al.* (1945), Macgraith *et al.* (1945), Fairley (1946)), paludrine cures malignant tertian malaria. The clinical condition of benign tertian malaria responds to a single dose of paludrine but, as with mepacrine, parasites reappear in the blood in three to eight weeks. It appears that doses of 0.1 gm. daily gives causal prophylaxis against malignant tertian and will suppress benign tertian malaria. Its toxic effects are negligible.

The problem as it remains to-day is the development of a true causal prophylactic capable of killing the malaria parasite at any stage.

### CHEMOTHERAPY OF SYPHILIS

The chemotherapy of syphilis and trypanosomiasis has from the beginning been closely identified. Not only was the first observation of the efficacy of atoxyl (*p*-aminophenylarsonic acid) made in a trypanosome infection (Thomas, 1905), but trypanosome infections have usually been used in the experimental chemotherapeutic studies. Thus the experimental studies from which first arsphenamine (Ehrlich, 1910) and then neoarsphenamine (1912) emerged were made with *Trypanosoma equiperdum* and not spirochaetes. Ehrlich advanced the widely accepted theory, based upon *in vitro* studies, that the activity of atoxyl was due to its reduction to a trivalent molecule. He also thought the trivalent phenylarsenoxide derivatives too toxic for use in man and preferred the still further reduced derivatives, among which was found arsphenamine (Fig. 2). His high hopes for the single effective sterilizing dose led him to name the new compound "Salvarsan," in the hope that it would prove the salvation of mankind, as far as syphilis was concerned.

In recent years Tatum and Cooper (1934) reinvestigated the properties of *m*-amino-*p*-hydroxyphenylarsenoxide (mapharside) and found it to be more active and less toxic than neoarsphenamine, because it is excreted completely in two days, while neoarsphenamine is eliminated much more slowly. It follows that mapharside must be given twice weekly and not once weekly as is neoarsphenamine. Clinical studies (Foerster, McIntosh, Wieder, Foerster and Cooper, 1935) have since endorsed the advantages of mapharside. At the present time mapharside is the most widely used arsenical in the U.S.A. in the treatment of early syphilis. The usual course of neoarsphenamine alternating with bismuth extends over many months, and usually less than half the patients who begin these courses persevere to the end. Even so the cure rate is not more than 80 per cent. (Marshall, 1944). The alternative therapeutic approach of employing intensive therapy for short periods has received much attention. At first neoarsphenamine was administered by continuous intravenous drip for about 13 hours daily for five days, during which time an average patient received 4.5 gm. of neoarsphenamine (Chargin, Leifer and Hyman, 1935). Latterly 1.2 gm. of mapharside

spleen, and was present in 31 of 120 cases of chronic miliary tuberculosis which they reviewed. The size of the spleen was usually slight or moderate, but in three cases it was so large that splenectomy was required to relieve the symptoms. Hickling has published the case records of two patients considered to have tuberculous splenomegaly accompanied by radiological evidence of miliary tuberculosis of the lungs. In these patients the radiological signs of miliary tuberculosis of the lungs disappeared following clinical cure by splenectomy. It is possible that these cases belong to the group of sarcoidosis with splenomegaly. The first case was a man aged 35 complaining of lack of energy, loss of weight, and winter cough with little sputum and no hæmoptysis. Massive enlargement of the spleen was the outstanding sign. There was also enlargement of the *inguinal lymph nodes*. Radiological examination of the lungs showed extensive miliary shadows throughout both lungs. Biopsy of an inguinal lymph node showed the changes of chronic tuberculosis. Splenectomy was performed and at operation a large number of enlarged lymph nodes were found in the abdomen; the liver appeared normal. Three months after the operation the patient felt well, the inguinal lymph nodes had disappeared, lost weight was regained and he had returned to work. Radiological examination of the lungs showed a considerable reduction in the extent of the shadows. Two years 10 months after the operation he was in excellent health and radiological examination of the lungs showed no notable abnormality and there was no clinical evidence of enlargement of the lymph nodes or liver. Microscopical examination showed that the splenic tissue was almost entirely replaced by tissue showing the histological features of tuberculosis, with typical focal arrangement but without caseation. Tubercle bacilli were not demonstrated.

The second case was a female, aged 34, who complained of abnormal tiredness, shortness of breath, and attacks of pain in the left hypochondrium. There was marked splenomegaly. A tentative diagnosis of *splenic anæmia* was made. *Splenectomy* was performed, large numbers of round reddish masses were found in the abdomen and the surface of the liver showed large numbers of yellow spots. Nine months later radiological examination of the chest showed extensive miliary shadows in both lungs;  $3\frac{1}{2}$  years after splenectomy radiological examination showed that these shadows had practically disappeared. The patient was in good health 5 years 8 months after splenectomy. Microscopical examination of the spleen showed that the structure was almost entirely replaced by tissue showing the typical histological features of tuberculosis, without caseation, and tubercle bacilli were demonstrated by staining methods.

In these cases splenomegaly is the dominating feature in the picture; pulmonary symptomatology may be entirely absent. Another important point is the necessity for radiological examination of the lungs in all cases of splenomegaly of doubtful ætiology. Attention has been called to

occurring in brain tissue, blood and skin of thiamine-deficient pigeons and arsenic-treated rats were similar, since in both there was failure to oxidise pyruvic acid which accumulated and could be identified. Further research pointed to a possible explanation which was that trivalent arsenic combined with two closely situated -SH groups of vital systems. An antidote, if found, should provide a similar system and result in a stable compound with arsenic. Dimercaptopropanol, when found, reacted in this way (Fig. 3).

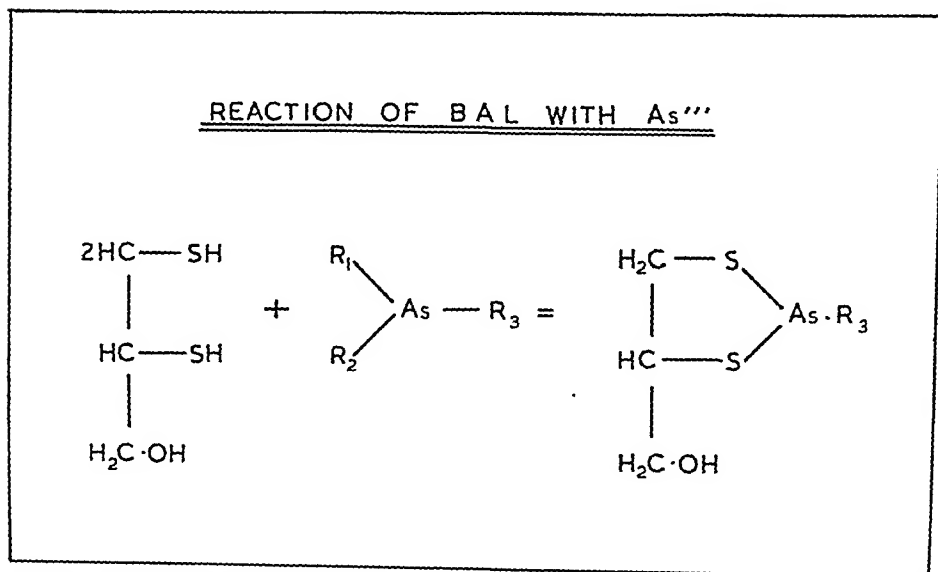


Fig. 3. Dimercaptopropanol (BAL) presents two closely situated reactive -SH groups with which trivalent arsenic compounds form stable unions. The resulting non-toxic complex is excreted.

Its application to the successful treatment of exfoliative dermatitis and other arsenic intoxications by the intramuscular injection of a 10 per cent. stabilised solution in oil (Waters and Stock, 1945) has been quickly followed by additional applications. It has been similarly used in mercury, antimony, bismuth, chromium, nickel, and gold poisoning.

The discovery of the therapeutic effect of penicillin against *Spirochaeta recurrentis* and *Spirillum minus* infection in mice (Lourie and Collier, 1943) offered a new hope for the chemotherapy of syphilis. Penicillin offered the possibility of realising the much sought after goal of successful intensive therapy of short duration with massive doses without fear of dangerous toxic effects. The first cases to be treated appear to be those of Mahoney, Arnold and Harris (1943) in the United States and the five years which have passed have not diminished the first high hopes of a curative drug. A recent analysis (1948) based on the treatment of half a million cases with penicillin quotes a failure rate in the treatment of early syphilis of 15 per cent. at the end of one year. As a result of this experience the following recommendations are made in the report. The

the similarity with Banti's syndrome and this is strengthened by the presence of hæmatemesis and ascites in certain cases.

*Uveo-parotid Fever.*—This clinical entity was described by Heerfordt in 1909 as a result of observations made during 1905-6 on three patients in the Copenhagen City Hospital. There were three essential and outstanding features in these patients, namely, enlargement of the parotid salivary glands persisting over a period of several months; inflammation of the eye involving the uveal tract; and a continuous fever of low degree. In two of these patients there were also cerebro-spinal paralyses. Heerfordt's communication was followed by a number of case reports, chiefly in the German and Scandinavian literature, and in 1924 Berg was able to collect a total of about 40 cases of the disease. Up to the year 1944 Stuart states that about 110 cases were described. In 1936 Bruins Slot suggested that the disease was a manifestation of sarcoidosis. Considerable discussion has occurred concerning the nature of uveo-parotid fever and whether the cause is tuberculosis, and this has extended to include the subject of the relations of tuberculosis to ophthalmic lesions in general. There is agreement amongst the various authors that the histological features are those of tuberculosis without caseation. The lesions show many giant cells within areas of epithelioid proliferation, some marginal lymphocytes and fibrosis. One observer performed a biopsy on an involved parotid salivary gland on two occasions with an interval of about seven months. The first section, taken during an active phase of the disease, showed typical tubercles without caseation; the second demonstrated massive sclerosis and shrinkage of the tissue with round cell infiltration.

It is now known that any structures in connection with the eye may be involved. Thus, cases of conjunctivitis, keratitis, iridocyclitis or more extensive uveitis have been described. Involvement of any, or all, of the structures of the eye is comparatively common during some stage of sarcoidosis and it may be the initial manifestation. There is a tendency to spontaneous recovery; death rarely occurs, and is due to miliary tuberculosis. Facial paralysis is stated to occur in half the number of cases. Pautrier has described the evolution of the disease in an interesting case report; the initial sign was bilateral parotitis, followed by facial paralysis, iridocyclitis, and multiple skin lesions. In some cases healing results in scarring and the formation of synechiæ; the sight may be destroyed and enucleation of the eye is sometimes necessary. Retrobulbar neuritis, resulting in blindness, has been described by Longcope; in five other cases enucleation was required, and in one of these both eyes were affected, resulting in total blindness.

Usually there is a period before ocular symptoms develop which is characterised by malaise, anorexia and fever ranging between 99° and 101·5°F. Cerebro-spinal nerve paralyses have been described frequently and the clinical picture may be modified considerably. The facial nerve

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## THE PORTRAITURE OF WILLIAM HARVEY

As announced in the *Annals* of September 1949, *The Portraiture of William Harvey* by Mr. Geoffrey Keynes, F.R.C.S., can now be purchased on application to the office of the *Annals of the Royal College of Surgeons*, or through booksellers, at a price of 25s. net.

is commonly affected on one or both sides. In one of Heerfordt's patients there was dysphagia with palatal and laryngeal paralyses.

*Treatment.*—Measures designed to improve the general resistance of the patient are instituted and there must be close collaboration between the ophthalmologist and radiotherapist. If the lesion is early, the nodules on the iris disappear with irradiation therapy in a few days or weeks; thereafter, further absorption of exudates occurs. Good results also occur with irradiation of the parotid salivary glands.

*The Syndrome of Mikulicz.*—In a number of cases reported in the literature there was enlargement of the lachrymal glands. In others there was an associated enlargement of the submaxillary and sublingual salivary glands in addition to uveo-parotid fever, simulating the features of the syndrome of Mikulicz, which was described in 1888. It may be that there is more than one etiological factor, including tuberculosis, concerned, and some of them may be due to sarcoidosis.

*The Pancreas.*—Nickerson has reported a case where lesions were present in the pancreas. These were relatively rare and solitary and found in the interacinous and intra-acinous fibrous tissue. There was no involvement of the acini or islets.

*The Testicle.*—Involvement of the testicle has been described by Pautrier, Nickerson and Longcope. In Nickerson's case lesions were few and solitary, occurring in the interstitial tissue. The seminiferous tubules were normal and spermatogenesis was unaffected. Longcope describes a case in which there was involvement of the testicle and epididymis with profound changes in the secondary sexual characteristics leading to a condition simulating eunuchoidism.

*The Kidney.*—Involvement of the kidney accompanied by extensive changes in the retina is uncommon, and this picture simulates glomerulonephritis. Cases are also reported in the literature with sarcoid lesions in the kidneys without symptoms. When symptoms are present, the patients usually conform to a definite pattern; the disease runs a relatively long benign course, there are minimal urinary symptoms with azotemia, anæmia, and the blood-pressure is usually normal. The degree of non-protein nitrogen retention with anæmia is out of proportion to the clinical evidence of renal disease. It is of interest to note that renal sarcoidosis has been described in association with hypertension. The renal insufficiency is caused by mechanical interference with renal function. Extensive retinal changes occur in sarcoidosis with or without renal involvement; the way in which these changes are produced is not understood. It is of importance that the underlying etiology in these cases is recognized, because the prognosis in sarcoidosis is usually favourable. In this connection the surgeon may play a part in the diagnosis, as instanced in an interesting case reported by Klinefelter and Salley, of a young soldier who developed nocturnal frequency of micturition. Other symptoms appeared gradually, including loss of weight, headache and impairment

£1000 is the Secretary five hundred pounds like annuities to the Royal Society for the prevention of Cruelty to animals one thousand pounds like annuities to the Royal Veterinary School of Medicine one thousand five hundred pounds like annuities the capital and income of such sum to be applied in or towards the establishment and maintenance or in or towards the establishment of three Schools to be respectively named Smith's School and Charity each School to be respectively situated at such places in the County of England as the Trustees or Managers of the last mentioned endowment shall think fit to the Royal College of Physicians one thousand pounds like annuities to the Royal College of Surgeons one thousand pounds like annuities and it is my desire and especial request that the last two legacies of stock to the Royal College of Physicians and the Royal College of Surgeons respectively may be the respective persons to whom my Executors may as soon after my decease have the same be placed in trust in connection with the said Colleges respectively and that the income therefrom shall yearly be expended in establishing and permanently maintaining an annual Lecture to be delivered in connection with the said Colleges respectively on Lectures to be chosen annually by the Presidents of the said Colleges respectively upon some subject connected with Physic or Surgery on the twentieth day of August in every year which day will be the anniversary of the death of my late Husband Doctor William Wood Brodshaw except when the said twentieth day of August shall fall upon a Sunday in which case such Lecture shall be respectively delivered on the following day each of which Lectures shall be delivered in honour of the memory of my said late Husband and be called The Brodshaw Lecture I direct my Executors and Trustees herein after appointed to stand possessed of the sum of One thousand pounds three pounds six pence in General and to pay annuities thereof yearly to distribute or to place in the hands of the Rector Churchwardens or Overseers of the Parish of Uppor Walsall in the County of Stafford or of some other respectable persons for distribution amongst poor persons being parishioners dwelling in the Parish of Uppor Walsall aforesaid the annual income of the said trust fund which distribution I direct to be made annually on or about the day and in which distribution I

Fig. 1. Facsimile of part of Mrs. Sally Bradshaw's Will.

Occasionally the Act. asteroides may affect the lungs. The only actinomyces which commonly gives rise to disease in man is the actinomyces bovis, or Israeli, which will only grow when oxygen is excluded or present in minimal amount. This common pathological agent, which is responsible for nearly all the lesions in man, has never been found outside an animal body. It has never been found on grasses or grains, on hay or on straw, and the farm-hand as such is not more likely to become infected than the city clerk. In man it often lies latent in the carious crevices of teeth or in the deep crypts of the tonsil. It is relatively as common in the peer as in the peasant, but strangely enough is more common in men than in women.

That the organism which is so frequently present in the body does not more often cause disease is due to the fact that it finds difficulty in penetrating normal epithelial surfaces; when by accident, disease or by necessary operation the epithelial surface is broken, the actinomyces



of vision. Four months after the onset of the disease, fever, retinitis, anæmia, albuminuria and azotemia with normal blood-pressure were found. It was not until six months after the onset that the diagnosis was made as a result of biopsy of an enlarged lymph node. Later, the fever, lymphadenopathy, and retinal changes subsided and the anæmia and renal insufficiency improved. The changes in the blood in these cases are important and the disease should be suspected when hyperglobulinemia and hypercalcemia are found in conjunction with azotemia. These changes may be present also in multiple myeloma.

*The Pituitary Gland.*—Several cases have been reported of diabetes insipidus due to involvement of the pituitary gland which was infiltrated with sarcoid. There may be also co-existing uveo-parotid fever.

*Other Organs.*—Attention has been called in the literature to involvement of other organs including the heart, thyroid, breast, skeletal muscles tendon sheaths, optic nerve and prostate.

*Conclusion.*—Finally, let us listen to the voice of Jonathan Hutchinson—"Surely teaching is the highest vocation of the human spirit. I mean training in the largest sense, helping the next generation to be better and to understand more clearly than we have done. I believe more and more firmly in the continuousness of life. Only I do wish that individual life was a little longer, and individual health a little more certain, and perhaps a few more changes might be introduced."

#### ACKNOWLEDGMENTS

I wish to thank my colleagues who kindly allowed me to study certain clinical aspects from their case-records—Professor D. W. Smithers, Dr. M. Lederman, and Dr. W. D. W. Brooks; I appreciate the help of Dr. R. A. Willis and Dr. Woodhouse Price in studying the Pathology; Dr. Campbell Golding in the Radiological aspects; and Miss J. Hunt who prepared my lantern slides.

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the colony usually known as the "sulphur granule." There was one type of fungus which formed less firm and more diffuent granules and these were found to be very sensitive to penicillin. Roberts, Tubbs and Bates in 1945 published an account of a case which was readily affected by penicillin and in that case they noted that the granules were very viscous and web-like rather than in a compact mass. So the firm "sulphur granule" appears to have a protective function on the contained fungus.

Whence comes the actinomycotic infection? We must put aside the traditional and popular fairy tale about infection from grass or straw, while admitting that many text-books are still doing their best for the older and fallacious teaching. Are we to consider it likely that infection comes from contact with the cow or from infected milk? There is very little, in fact negligible, evidence of this. The disease is so rare in other animals that we need not consider this source. We have only one possibility left—infection from one human being to another. Apart from one striking case in which infection probably took place by the contact of kissing, there is no evidence for direct contagion. We are forced to the conclusion that infection with actinomycosis takes place by indirect means. Professor Wilkinson has told me of one case in which infection apparently was conveyed to a patient from another patient in the same ward who happened to be the victim of the disease, but ordinarily infection may come not from a diseased person but from a carrier. The organism frequently exists in the crevices of carious teeth, and it needs little imagination to see how many opportunities there are for the organism to pass from one person to another. The carious tooth is the usual place from which the trouble springs. Let us now follow the actinomyces in its journey to one or other part of the body from its favourite haunt in the mouth.

As one would expect more than half of all the cases occur in the immediate vicinity of the jaw, in the jaw itself, the cheek, the submaxillary and submental regions, and the neck. To emphasize the connection between infection and the carious tooth I would mention the case of a young woman whom I treated 30 years ago for a large cyst of the lower jaw which gave egg-shell crackling; the fang of a carious tooth was in the roof of the cyst which was filled completely by actinomycotic pus.

When once the fungus has obtained lodgement in the mouth it is inevitable that from time to time portions will be swallowed and pass through the alimentary canal. In most cases no harm results but in areas where it may meet an ulcerated surface, or when inflammatory processes give it an opportunity to extend, it may cause serious trouble. It may form a granuloma in the wall of the stomach and several cases have been recorded in which partial gastrectomy was performed under the impression that the condition was a cancer. A number of cases of infection of the peritoneum or of adjacent viscera have followed the perforation of a gastric or duodenal ulcer. One case has been recorded

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# SOME UNPUBLISHED LETTERS OF WILLIAM CLIFT RELATING TO JOHN HUNTER'S DEATH

by

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WHILE OCCUPIED IN perusing and investigating the Owen Collection of Letters housed within the precincts of the Natural History Museum, South Kensington, I came across three letters written by Owen's father-in-law, William Clift, to his sister, Elizabeth Clift, living in Bodmin, Cornwall. Inasmuch as these letters were written very shortly after Hunter's death and do not appear to have been unearthed or at any rate published before, I thought that they may not be without interest to readers of the *Annals of the Royal College of Surgeons of England*.

One letter from Castle Street is actually dated October 18, 1793—two days after Hunter's death, and affords some information concerning Hunter's movements between mid-day when he left his home in Leicester Square and his arrival at St. George's Hospital. Since the Hospital Board Meeting which he set out to attend was timed to commence at noon, and Hunter did not leave his house till twelve, and some time must have elapsed before Clift, probably running, reached Charles Street, St. James's Square (now Charles II Street) from Leicester Square, it is submitted that Hunter arrived quite late for the St. George's Hospital meeting. The fact that Hunter's name does not appear with those attending the meeting is also suggestive of his late arrival, probably only the names of those present at the commencement of the meeting being mentioned in the minutes. Perhaps the flurry of being late, in addition to being thwarted by his colleagues at the meeting, may have played a part in inducing the fatal attack of angina.

Hunter is sometimes said to have just managed to struggle from the Board Room into an adjacent room before expiring in the arms of a medical colleague, but Clift, writing two days after the event states that Hunter "died in an hour or two." Presumably the sedan cortège left St. George's about 4 p.m., if Hunter's body did not reach Leicester Square till 5 p.m.

Clift also writes that Mrs. Hunter, the son and daughter were living at Brighthelmstone (Brighton) when the tragedy occurred, and did not return till the next day (October 17).

Friday October 18th, 1793.

DEAR SISTER,

I have now taken pen in hand to write but am at a loss for words to express my ideas—what I am going to tell you when I say that Mr. Hunter went from our house at 12 o'clock on Wednesday morning as well as ever I saw him—and the Butler came and beg'd me to run after Mr. Hunter with his round (which is a paper that Mr. Hunter used to put down all the places upon that he had to call at, till he came home in the evening), and I overtook him in Charles St.,

St. James Sq. where I saw him get into his carriage as well as ever I saw him in my life, where they then drove to St. Georges Hospital where there was to be a general Board held and Mr. Hunter had not been there very long before he was taken very ill and died in an hour or two. I believe our people would not like to have it known that he died till he was brought home which was about 5 o'clock in the evening, in a Sedan Chair.

All our family was at Brightelmstone at the time where Dr. Baillie went that night and got there in the Morning and they all came home last evening\* except some servants who are left take care of the things left behind . . . Mrs. Hunter and Miss and Mr. John are almost breaking their hearts. . . .

Mr. Home was forced to go to Deal last evening before Mrs. Hunter came home and will not be back till to-night,\*\* he went to see some of our soldiers that are come home from France wounded. I am afraid our house will be turned quite upside down now the wall and support is gone. I shall know how it is to be with me in a fortnight or so I suppose when all things are settled a little but I do not care how it is to be. I hope God will provide for us.

I should like to live in London very much but I dont think I shall ever like any Master as well as Mr. Hunter. Perhaps Mr. Home might take me to serve out my time with him to look after the dissecting rooms but then all my future hopes of learning to draw would be quite put a stop to, and I suppose I should never learn Anatomy under him, for he is quite a different man from Mr. Hunter as Mrs. Gilbert well knows.

LONDON,

Friday October 18th, 1793.

Some information concerning Hunter's funeral is forthcoming in a letter of Clift, dated November 20, 1793, in which he also tells his sister that the horses and carriages were already sold and the coachmen, footmen and butler discharged.

Clift saw the coffin of his master deposited in the vault in St. Martin-in-the-Fields, perhaps the last interested person to gaze on it till it was re-discovered by Frank Buckland over half a century later.

November 20th, 1793.

"I deferred writing till now for I did not see Mrs. Hunter since she came from Brighton till a few days ago, and she told me that I need not make myself uneasy about anything for I should be taken care of and that she had wrote to Mrs. Gilbert and received her answer and that I should stay with her till she heard of something better for me, and that I should not want a friend as long as she did live—Mr. Hunter was buried on the 22nd October at St. Martin's Church. It was a very private burying for there was only a Hearse and two Coaches, besides Mr. Hunter's chariot, but nobody rode in that; my cloaths was not made soon enough to go to the Burying and none of the servants went to the burying but I was acquainted with the undertaker and so I went to the Church and he put me into the vault with him—none of our people saw me there I believe and I did not want them to. Mr. Hunter's coachman and footman and the Butler are discharged, and Mrs. Hunter's coachman, for the Both

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\* October 17.

\*\* October 18.

carriages and Horses are sold, and the Horses at the Country house are sold and since Mr. Hunter's footman has gone I have had to go to all Mrs. Hunter's acquaintances with cards, and yesterday I was out at Earls Court with Miss Hunter and the Lady's maid to pack up some books and things to bring to town —I think it must seem very strange to Miss Hunter to ride in a Hackney coach, being used to ride in one that was reckoned the handsomest coach that was at court when Mrs. Hunter had it to go to court in.

I have got a new suit of cloth brought home only a week before Mr. Hunter died and now I have a suit of black clothes and a new hat. Not over 2 months ago I had 6 new shirts and this week I am to have some new pocket handkerchiefs."

Another letter also written to the same sister five months after Hunter's death bemoans his own miserable board-wages, seven shillings a week, a lament which re-echoes in many letters and to which I may return on some subsequent occasion.

On the subject of the marriage of Hunter's daughter Clift writes with little delicacy, "calling a spade a spade."

To. Miss Elizabeth Clift,  
Bodmin.

March 16th, 1794.

"I was down at Blackheath last Sunday week to see Mrs. Hunter, but she did not say anything to me about a place, nor did not give me anything to put in my pocket, she never gave me as much as sixpence as yet, and now I am obliged to pay for my own letters now she is out of Town. I shall enquire soon who is to pay for them as they never give me any money they can't expect that I can pay for them.

There is only the housekeeper\* left in the front house to take care of it till it is let and her and I, am on board wages. She gives me a shilling now and then for picket money but she might afford to give me a shilling a week, if she had a mind, for I believe I have 7 shillings a week.

Mrs. Hunter don't keep any carriage now, and only keep a ladys maid a footman, and a maid of all work. They have a pretty little house and garden and it is about 6 miles out of Town.

Miss Hunter is to be married to one Captain Cambell—I think for my part they have made too much haste about it so soon after the poor old Mans death—Everything has been getting ready there for some time past, and the Bed and all is ready for them to get into I believe—"

It is with pleasure that I accord my thanks to the Trustees of the Natural History Museum for permission to publish these letters and to Mr. Cockburn Townsend, the Librarian, for his unfailing help and courtesy.

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\* Mrs. Adams.

# SOME PROPORTIONAL WEIGHTS AND MEASUREMENTS OF THE HUMAN BODY

by

Professor F. Wood Jones, D.Sc., F.R.S., F.R.C.S., and the Staff of the Anatomical  
Department, Royal College of Surgeons of England

ALTHOUGH THE WEIGHTS of the human viscera are recorded at autopsy as a matter of routine and there is a mass of data on the subject readily accessible, when information is sought as to the weights and measurements of other systems and parts relative to each other and to the entire body, no authoritative literature appears to be available. Twice in my personal experience it has been important, for medico-legal purposes, to make some estimate of the weight and height of an individual of whom no more than a dismembered part was available. In neither case was there any published data upon which such an estimate could be based. The question has been raised again recently in connection with certain criminal proceedings and again a search of the literature has failed to produce the facts necessary for arriving at a definite conclusion. Under the circumstances, the kind offices of H.M. Inspector of Anatomy were sought and, at the outset, his wholehearted cooperation in the matter is gratefully acknowledged. Two cadavera, a male and a female, were placed at our disposal for the purposes of the enquiry. No preservative reagents were employed and the necessary operations, which had been planned in advance, were completed satisfactorily only by the unremitting and co-ordinated efforts of the staff of the Anatomical Department. The whole mass of data accumulated must await full publication elsewhere, but meanwhile it has been thought best to make available, in the form of percentages some of the relative weights and measurements averaged from the examination of the two cadavera. Few details of technique need be described here. It was decided to dismember the cadavera in the manner in which it might be supposed that an individual whose aim it was to dispose of a corpse would set about the business. To this end, the limbs were abducted and incisions were carried through the tensed adductor muscles to the joint and were then continued in the same line after the joint had been disarticulated. The head was removed at the occipito-atlantal joint. The tongue, larynx and trachea were included with the thoracic viscera. Both subjects were aged and of small stature. The male, aged 70, weighed 43,191 grammes and was 166.5 cms. in standing height. The female was 89, with a weight of 29,478 grammes and standing height of 146.5 cms.

In the absence of any corresponding data derived from younger and more robust subjects, the following percentages must, therefore, be

regarded only as those applying to the aged. It is much to be hoped that at some future date the investigation may be carried further afield in order to render the results of more universal application.

WEIGHTS					
Proportion of					%
LIMBS	to body weight	..	..		38.17
HEAD	" " "	..	..		8.56
TRUNK	" " "	..	..		53.36
UPPER LIMB	" " "	..	..		4.82
LOWER LIMB	" " "	..	..		14.26
SKIN AND SUBCUTANEOUS TISSUE	" " "	..	..		14.55
MUSCLES	" " "	..	..		38.89
BONE	" " "	..	..		25.1
ABDOMINAL VISCERA	" " "	..	..		11.47
THORACIC VISCERA	" " "	..	..		6.08
CRANIAL VISCERA	" " "	..	..		3.2

MEASUREMENTS					
Proportion of					%
UPPER LIMB	to height of body	..	..		44.26
LOWER LIMB	" " " "	..	..		50.01
HEAD (vertex to chin)	" " " "	..	..		15.0
TRUNK (suprasternal notch to perineum)	" " " "	..	..		36.7
ARM	to length of upper limb	..	..		42.93
FOREARM	" " " "	..	..		30.09
HAND	" " " "	..	..		27.46
THIGH	to length of lower limb	..	..		51.47
LEG	" " " "	..	..		40.23
HEIGHT OF FOOT	" " " "	..	..		9.7
LENGTH OF FOOT	" " " "	..	..		28.3



# REPORT BY THE DIRECTOR OF THE IMPERIAL CANCER RESEARCH FUND

Professor W. E. Gye, M.D., F.R.S., F.R.C.P.

THIS REPORT DEALS chiefly with a long-continued, difficult, uncertain and finally successful research on the propagation of tumours of mice with dry tumour tissue.

The reasons justifying such persistence in work which often appeared hopeless and was naturally costly lie in the history of cancer research.

It is now well known that there are two sorts of tumours with a strange fundamental difference between them, namely the group, comprising all the tumours of small mammals and therefore presumably of human beings, which can be propagated only by grafting living cells under the skin of an appropriate animal; and a small exceptional group, almost all sarcomas of the domestic fowl, which can be propagated both by inoculating living cells and by injecting either cell-free filtrates or dried tumour tissue. The early work of the experimental period of cancer research was carried out with the tumours of small mammals, and the results achieved led to opinions which still determine current lines of thought and research.

It was found by the pioneers of cancer research, Jensen, Bashford, Ehrlich, Leo Loeb, Borrel and many others, that a spontaneous tumour of a mouse, carcinoma or sarcoma, can be transmitted to another mouse by implanting a small mass, a piece as big as a large pin's head, under the skin. The piece of tumour thus grafted consists of malignant cells and a supporting framework of blood and lymph capillary vessels and connective tissues; this supporting framework is known as the stroma of the tumour. Microscopic analysis of the process of grafting showed that the normal tissues of the stroma rapidly die, that many of the malignant cells in the centre of the clump of cancer cells die also, that the new host provides a new stroma on which the peripheral surviving cancer cells establish themselves, grow and multiply and form a second or "daughter" tumour. Bashford in the Annual Report for 1904-05 wrote, "Cancer can only be transmitted experimentally by processes which allow of the continued growth of the tumour of one animal in other animals of the same species." This generalization led him to conclude that "it is not permissible to seek for the cause of cancer outside the life processes of the cells."

Since the method of propagating cancers is of this nature, merely grafting not in any way related to an infection, it is to be expected that mouse tumours will "take" or grow only in mice, rat tumours in rats, rabbit tumours in rabbits, and so on. Many attempts have been made to transfer human cancer to animals and as we should expect, all have ended in failure.

Experimental cancer research began at the start of this century, just after bacteriology had achieved some of its most spectacular successes.

Naturally cancerous tissues were examined for bacteria and experiments were made to decide whether tumours could be transferred with tissue extracts from which all living cells had been removed. All such efforts ended in failure. Even when ordinary filter papers were used to obtain filtrates it was proved that no extract from which red blood corpuscles had been removed by filtration would give rise to another tumour. Thus it was, and is now, certain that cancer is not of the nature of a bacterial infection. In tuberculosis, for example, we can demonstrate the tubercle bacillus in the diseased tissues and we can transfer the human disease to guinea-pigs, monkeys and rabbits. With cancer we can do none of these things; the more deeply and extensively cancer research was carried by Bashford and his contemporaries, the more certain it appeared that the histopathological findings of human pathologists of the nineteenth century, and particularly those of Ribbert, were correct. A meticulous study of tumour metastases in human cancer led Ribbert and his followers to believe that cancer grows "aus Sich heraus," that is from its own resources by growth and division of the malignant cell and never by any sort of spread from a malignant cell to normal cells. The exceptions to this rule which other pathologists published were few in number and interpretation was difficult. Bashford and most pioneers of experimental research had no hesitation in accepting Ribbert's views concerning the pathological nature of cancer. Hence the statement that it is inadmissible to seek for the cause of cancer outside the life processes of cells, appeared to be completely reasonable.

It is important at this point to comment upon the use of the word "cause," as used by Bashford. In common with most students at this early period, Bashford meant by this word the "continuing cause." It had been known since 1775 that soot from chimneys caused cancer of the skin; Bashford himself added the Kangri basket and betel-nut preparations to the list of causes. But these causes, perfectly definite and genuine, do not account for the continuation of a tumour once a tumour is started. The sense in which Bashford used the word was quite different; he referred to the "cause" or "explanation" of the properties of a growing cancer. In the end he concluded that cancers are "causeless," since no agent, separable from the living cancer cell, could be obtained. Consequently, when Peyton Rous' discovery was made in 1911, that some tumours of fowls can be propagated by the simple injection of a cell-free extract of the tumour, he was not prepared for such a strange revolutionary new fact; nor was anybody else. Rous' discovery was of cardinal importance but was neglected for many years because of previous negative experience. Moreover, the strange property of species and cell specificity, of the active agent, the virus, of a filtrable tumour appeared to warrant the scepticism inherent in the common description of these new tumours as being "a disease sui generis."

Thus, the negative results of all attempts to demonstrate a cause—virus or other—in tumours of mice, rats, rabbits and human beings was

accepted and allowed to guide the course of cancer research ; the positive finding with a small number of avian tumours—now not so small, being well over 200—was neglected. The aphorism of the great William Harvey, that in science it is best to proceed from the known to the unknown, was ignored. One of the unfortunate consequences of this choice has been the widespread growth of speculation concerning the continuing cause of cancer. The most favoured speculation assumes' that a cancer cell is a somatic mutation of the corresponding normal cell, a purely verbal explanation in which an attractive word with a definite meaning in other contexts is used to cover up our ignorance. At least it can be said that if by this term is meant that in a normal cell when it becomes malignant the genes have undergone an alteration which brings about cancer, the hypothesis cannot be tested by Mendelian methods, since cancer cells multiply asexually and any hypothesis which cannot be tested and lead to fresh knowledge is not very valuable. Moreover, the hypothesis ignores the natural history of cancer which would, if mutations of cells play a part in cancer, compel us to postulate a succession of mutations ; which is absurd.

In the early years of the Fund's existence it was not known how to start tumours in animals from scratch. The first success in this new form of research was achieved by Clunet, who succeeded in inducing tumours in rats by application of X-rays. To-day we know many ways of initiating new tumours. A mouse, for example, can be painted on the skin with a solution of one or other of dozens of pure chemical substances, and three to twelve months later cancer of the skin may ensue ; or the chemical substance, dissolved in a suitable oil, may be injected under the skin and at a later date, possibly months later, a cancer of the subcutaneous tissues may form. Likewise tumours may be started afresh by treating man or animals with X-rays or radium emanations. Most of the pioneers of X-ray therapy succumbed, after many years of skin trouble, to skin cancers started by radiations. All these tumours, started either by chemical substances, physical forces, or by gross parasites, can, under permissible suitable arrangements, be propagated from animal to animal by implanting small fragments of living tumour cells under the skin of animals of the same species and variety as the original animal which bore the primary tumour. But from the daughter tumours, which are, as Bashford pointed out repeatedly, lineal descendants of the original tumour cells, the chemical or physical agent which started the tumour is not recoverable. This is perfectly illustrated by a tumour, known as C 48, in the Fund's laboratories. This tumour is a sarcoma of the inbred strain of mice known as C 57 Black. Mice of this strain were injected under the skin late in the year 1941 with small doses of the pure chemical compound known as methylcholanthrene. After a few months tumours appeared at the site of the injected chemical. One of these was taken out aseptically and tiny fragments, each the size of a pin-head, were implanted under the skin of half a dozen normal C 57 Black mice. Each fragment grew and formed a

"daughter tumour" and the best of these tumours was again used to start a fresh series of tumours. The serial number of the transplantations at the time of writing is 156. This tumour represents in a simple form the crucial problem of cancer causation. No rational man knowing anything about the occurrence of such tumours in this strain of mice could doubt that the tumour was started by the action of the pure chemical substance on the tissues in the area in which the oily solution was placed; but, further, no rational man could believe that the continuing growth in a series of mice over a period of 7 years is due to the continued action of the original milligramme of methyl-cholanthrene. The "cause" or "explanation" of this continued independent growth of the tumour, growth which can apparently go on for ever, is the central problem of the ætiology of the disease. So far as tumours of mammals are concerned, no agent has hitherto been detected in the tumour cells with which a new tumour can be started, nor can any trace of the original chemical substance be recovered from subsequent daughter tumours. In the filtrable tumours of chickens the agent which is responsible for the continued growth of tumours is known and the situation is quite different. An extremely small dose, as little as a thousandth of a cubic centimetre, of a 4 per cent. cell-free watery extract of a tumour is all that is needed to start a new tumour; the new tumour is palpable in a few days and reaches a large size in two to four weeks. From this tumour cell-free extracts can be obtained and the process repeated. The agent, a virus, multiplies as the tumour cells multiply. Thus, unlike the chemical substances, radiations or gross parasites which can *start* a tumour and, once the tumour has started, are no longer necessary for the continued growth and multiplication of the malignant cells, the virus particles multiply and are obtainable again and again in large quantity and retain the power to start a tumour afresh. They have a different function in cancer; they are the *continuing* cause of the tumours in which they can be demonstrated.

The pioneers of cancer research, men like Jensen, Bashford, Ehrlich and Apolant, recognized from the beginning of cancer research that cancer causation is divisible into two parts; first, the remote causes like coal-tar, soot or X-rays which act in a way which is still mysterious to prepare tissues for malignancy, and secondly, the intracellular or continuing cause which maintains cancer cells and in an unknown way stimulates them to divide. Cancers may have one or other of many remote causes; we know of only one intracellular cause, the virus found in certain tumours. It is because of the manifest importance of the project that for many years systematic endeavours have been made in the Fund's laboratories to passage mouse tumours with dried tissue or with cell-free extracts; in other words, to bridge the gap which appeared to be unbridgeable between tumours of the domestic fowl and tumours of the small mammals.

In the history of cancer research there are two observations, both made before the first world war, which were always difficult to fit into the

general set of opinions or theory which guided research. The first observation is that occasionally, but not very often, a breast cancer in laboratory stock mice, that is mice which breed indiscriminately, develops a sarcoma of the connective tissues of the stroma of the mammary cancer. This discovery was made independently by Bashford and Ehrlich and was examined in great detail in the Fund's laboratories by Haaland and in Frankfort by Apolant. Careful histological research supported the conclusion that the sarcoma was derived from the connective tissues supporting the growing cancer and that the malignant transformation was presumably due to some influence of the adjacent malignant epithelial cells. There can be little doubt now, and especially since Dr. Ludford's recent investigations with the technique of tissue culture, that this is the correct explanation. It is very difficult to maintain, with the knowledge now at our disposal, that no agent, such as a virus, is present in the mammary cancer cells, for the alternative explanation would, as the late Professor Boycott said, commit us to a belief that the connective tissue cells were merely copying the bad habits of their neighbours; the problem of cancer would become a moral problem.

Since the discovery of this phenomenon forty years ago, a great deal of fruitful work has been carried out in inbreeding of mice; we now have many practically homozygous strains, some with high, others with very low incidence of cancer of the breast. In some, e.g., the C3H, Strong A and R 3 strains, the incidence of breast cancer may be as high as 90 per cent. in the females. The relevance of spontaneous cancer in inbred mice to the subject of malignant transformation of supporting connective tissues consists in the fact, now well established, that although sarcomatous transformation in mammary cancers of laboratory stock mice is rare, in the high cancer inbred strains it is common. The fact was first observed in 1936, so far as we are aware, by Dr. P. A. Gorer, then working at the Lister Institute. Gorer's observations have been confirmed in the Fund's laboratories, in the Institute for Cancer Research at Bethesda and elsewhere.

Inbreeding of mice, to get either a high percentage of breast cancer or a low, has naturally attracted world-wide attention. The work was begun in the Fund's laboratories more than forty years ago by Dr. J. A. Murray, F.R.S., in experiments designed to determine whether heredity plays any part in the occurrence of mammary cancer; the enormous extension of the work, which led to the discovery by Bittner of the milk factor, has been done almost entirely by our American and Dutch colleagues.

In our own investigations we have adopted as our working hypothesis that consideration of inbreeding to get high or low incidence of cancer as simply a part of genetics is not likely to be fruitful; this is self-evident in the light of the demonstrated complexity of the phenomenon. But we have gone further. We regard the whole process of inbreeding for tumours, not as inbreeding for a unit character but as a process of selection

by breeding of the most active variants of the milk factor, which most students now agree is a virus. When brother-sister mating is carried on in a high cancer line without special attention being paid to the incidence of mammary cancer, the incidence of cancer falls steadily, from 90 per cent. to 40 or even to 20 per cent. This fall in the cancer rate is not brought about by alteration of the genetic constitution of the animals but, as has been shown by W. S. Murray, by a change in the "tumour inciter." We regard the high incidence of stromal sarcoma as being due to the occurrence of new active strains of the virus brought into existence by selection. This conception of the plasticity of viruses is in accordance with all we know of viruses in general, for of all disease agents at present known, they give rise most easily to variants.

The second observation to which attention must be directed was made by Ehrlich and published in 1907. It is that a mammary cancer of a mouse (the Ehrlich adeno-carcinoma) can be kept at a temperature of  $-8$  to  $-10^{\circ}\text{C.}$  for two years and retain its power to start tumours again when inoculated under the skin of mice. This astonishing observation made practically no impression on the course of subsequent research. In our own laboratories no repetition of the work was attempted and the only paper published on the subject of maintaining tumour tissues at a low temperature was not published until 1929. This paper was by our late colleague, William Cramer, in the 9th Scientific Report. Ehrlich's results have been confirmed by every student who has repeated such experiments, though none has kept tissue as long as two years. We ourselves have kept both carcinoma and sarcoma tissue for periods of time ranging from six to 12 months at a temperature of  $-79^{\circ}\text{C.}$  and have found that such tissues, maintained at such low temperatures, start new tumours again as readily as, usually more readily than, corresponding fresh tumour tissue which has been kept alive throughout the long period by the process of grafting.

Why had the Ehrlich discovery such little effect on the course of cancer research? It is very difficult to believe that delicate mammalian cells can withstand such low temperatures for so long and survive. Certainly embryonic cells which have as great "growth energy" as malignant cells, cannot. This has been proved by Miss Mann in the Fund's laboratories in the following way. Embryonic tissue of a homozygous strain of mice when minced and grafted into normal mice of the same strain not only survives but grows and forms large masses, as much as a gramme from a tiny fragment, which persist for months as embryomas. When minced embryonic tissue is exposed for even so short a time as three hours to a temperature of  $-79^{\circ}\text{C.}$ , and is then grafted into mice, no growth and multiplication of the grafted cells occur, no embryoma is formed. Microscopic examination of the graft of the refrigerated tissues shows as a rule a few surviving cartilage cells, but the softer tissues are all dead. When this kind of experiment is repeated with malignant tissue—mincing the tissue with scissors or a mincing machine, subjecting

the mince to a temperature of  $-79^{\circ}$  C. for three hours, inoculating the tissue into mice and then examining the graft at intervals from two to seven days—it is difficult to find a normal cell. Occasionally it is possible to detect one and from this a daughter tumour may arise. But histological examination cannot give a decisive answer to the crucial question: is the tumour which forms after prolonged refrigeration a new tumour or merely a continuation by grafting of the old? All previous investigators except Cramer have declared unequivocally that malignant cells survive such drastic treatment, though none has produced satisfactory evidence for the conclusion. Why is this most improbable conclusion preferred? It is almost certainly because the work which had been carried out by the earliest investigators—C. O. Jensen, Bashford, Ehrlich and many others—had failed to discover the existence of any continuing cause in the tumours then available for investigation; hence, to admit that tumour cells were killed by refrigeration and still retained their power to start tumours again would have been a strange revival of the “infective theory” of cancer. The whole subject had become bedevilled by dogmas, all based on negative evidence, and usually expressed in striking phraseology. Ehrlich himself, one of the greatest investigators of the last hundred years, advising a young man wishing to work at cancer, made the remark that he had wasted 15 years of his life in that way, and that “until some fundamental discovery has solved the mystery of life itself our knowledge of cancer will not advance a single step.” It is difficult to believe that men like Ehrlich or Bashford would have fallen victims to such mysticism and irrationality if the filtrable tumours had been included in their early investigations. The dogmas of such great men have spread throughout the scientific world, have dominated world opinion and intimidated bold original thought.

In collaboration with Dr. James Craigie, F.R.S., Dr. A. M. Begg and Miss Ida Mann, F.R.C.S., we have re-examined the effects of low temperatures on tumour tissues. Sarcomas of mice, rats, guinea-pigs and hamsters; carcinomas of rats and mice; and sarcomas of hens have all been maintained at  $-79^{\circ}$  C. for lengths of time varying from a few hours to a year.

An intensive investigation by Dr. Craigie of the survival of activity in tumour tissue frozen on  $\text{CO}_2$  ice has been undertaken with two objects in view. The immediate object was the development of a reliable technique of long-term preservation of transplantable tumours so that material might become available for certain projected studies on changes which may occur in the course of prolonged serial transplantation of tumours. Changes such as transformation from carcinoma to sarcoma, or loss of strict specificity of a sarcoma for the pure line strain of mouse in which it originated, raise questions of fundamental importance in regard to the continuing cause of cancer. Many serial transplantations over a period of years may be required before such spontaneous changes occur. Thus many generations of animals and a much greater number of tumour cell

generations are involved. Obviously, therefore, the question of whether the explanation of the observed changes is to be sought in the pedigree of tumour cells, or in the "continuing cause," or in a minor genetic change in the pure line mice used to propagate the tumour, cannot be answered with certainty, unless it is possible to compare, simultaneously in the same test animals, the tumour before and after the change. Such comparisons will become possible only when there has been elaborated a sufficiently exact and reliable method of preserving tumour tissue in a state of "suspended animation," without cell division, over a period of years.

The second objective of Dr. Craigie's study of the survival of tumours in the frozen state arises out of considerations of the possibility that a virus-like agent may be involved.

With few exceptions the recorded observations on survival of tumours at low temperatures have been made with relatively large masses of tumour tissue. Judging by our own experience, which is supported by the few reports available of similar kinds of work, we should expect that very finely minced tissue would be less able to survive freezing if activity of frozen material depends solely on cell survival. *A priori*, it would be expected that conditions favouring cell survival are more likely to be found in the centre of a substantial mass of tumour tissue than at the periphery. One essential specification of the method of preserving tumour tissue for the purposes which have been outlined, is that the tissue be reduced to a state of subdivision sufficiently fine for distribution in a series of vials before freezing. Exact quantitative work cannot be carried out if there are dissimilarities between different vials, or between small volumes (0.1 c.c.) of suspension obtained by thawing and diluting the contents of a vial. This problem of homogenization of tumour tissue has been solved by Dr. Craigie by the development of a tissue mincer of new design, which reduces tumour tissue to a suitable dispersion of single cells and groups of cells small enough to pass easily through the finest inoculating needle (No. 26 gauge).

In the early phase of this study on the survival of tumours through freezing and thawing, detailed attention was given to the question of eutectics of the physiological salt solutions used for suspension of the minced tissues before freezing. The simplest of such solutions is a 0.85 per cent. solution of sodium chloride which provides an approximate balance with the concentration of inorganic salts in blood. When a weak saline solution is frozen, ice crystallizes out and salt becomes concentrated in the interstices of the crystals reaching a concentration of approximately 30 per cent. This brine does not freeze solid until the eutectic temperature of  $-21.1^{\circ}$  C. is reached. Ringer or Tyrode solutions, which are more favourable to cell survival at normal temperatures, contain calcium chloride and this salt, which alone is highly toxic to cells, has a eutectic concentration of 48 per cent. at  $-51^{\circ}$  C. Theoretically, therefore, it might be expected that fine tissue suspensions frozen in physiological salt



solutions would be completely inactivated, but investigations by Dr. Craigie failed to confirm this. It might be mentioned at this point that the viruses of the fowl sarcomas withstand such strong concentrations of salts.

A variety of suspending fluids have been tested, with results which appear to be inconsistent with the notion that survival of activity after freezing and thawing can be explained solely on the basis of cell survival. Fluids which might be expected to inactivate fail to do so, while others which might be expected to favour cell survival cause inactivation. To quote an extreme example—a tumour suspension frozen in a dilution of 1 in 17.5 in 10 per cent. dextrose and 40 per cent. glycerine for 38 weeks produced tumours visible in five days in all of 12 mice when thawed and diluted 1 in 4 and injected in a 0.1 c.c. dose.

The best suspending fluid so far found for the preservation of all suspensions on freezing is dextrose in a concentration of 5 to 10 per cent. Dextrose is a substance which favours the survival of certain delicate bacteria when they are frozen and dried in the frozen state; but it would not be expected that dextrose would have a noticeable protective effect on tumour cells. Indeed, cytological studies have revealed intracellular changes in cells suspended in dextrose and these changes cannot be correlated in any way with any known facts to provide an explanation of survival. The degree of activity of frozen tissue is of a high order; for example, tumours have been obtained with the equivalent of as little as 1/100 mgm. of tumour frozen in a dilution of 1 in 50 in 10 per cent. dextrose.

In concluding this reference to Dr. Craigie's work it may be said that although the objective of developing a reliable technique of preserving tumour activity for quantitative studies has been reached, many puzzling facts requiring further study have been elicited. It is obvious that a great amount of careful and exact quantitative work will be required to elucidate the nature of survival of infectivity on freezing and thawing.

From the whole mass of work which has been carried out by Dr. Craigie, Dr. Begg and Miss Mann, it seems likely that not a single tumour cell survives freezing for months or even weeks and it is therefore impossible to conclude that the activity of frozen tissue is dependent on surviving cells. The observations of Miss Mann, with minced embryonic tissues and the violent activity of dispersed tumour cells suspended in 40 per cent. glycerine and kept for 38 weeks at the temperature of solid CO<sub>2</sub>, are difficult to reconcile. Similarly, the fact that freezing suspensions of tumour cells for a few hours at  $-79^{\circ}$  C. kills all or nearly all the cells, as is revealed by serial sections of early stages of grafts, does not fit in with the observed fact that such suspensions maintained for 12 months at low temperatures may start tumours more readily than equal quantities of cell suspensions of the fresh tumour, in which the majority of cells are living. To believe that the six or 12 months' frozen tissue contains one or two or fifty surviving cells would automatically involve us in believing that

these cells, though few in number, are much more active than the many thousands of fresh living tumour cells.

We are well aware that unless tumours which have hitherto resisted propagation with dried tissue, or with cell-free filtrates, can be so propagated by new techniques, the dogma that tumours are "causeless"—in Bashford's sense of the word—will remain unshaken.

We therefore turned to attempts to obtain active dry tumour tissue. Most of our work has been carried out with three mouse tumours, the origin of which must now be given.

1. The first is the sarcoma, labelled in the laboratories as C 48, which has already been referred to. It was started in 1941 by injecting subcutaneously small amounts, about 1 mgm. in all, of an oily solution of pure methyl-cholanthrene in an inbred line of mice, C 57 Black. One of the tumours which appeared as a consequence of this injection of the chemical compound was removed aseptically and transplanted into six normal C 57 mice. Each graft grew and the process has been repeated now nearly 200 times. The tumour is a soft rapidly growing sarcoma, of high malignancy. Many attempts have been made to transmit the tumour with dead dry cells, with extracts which have been centrifuged to clear the extract of living cells, and with Berkfeld candle or collodion film filtrates; all proved ineffective. The tumour is thus typical of the usual mouse or rat cancer, and the "logical" deduction of any but the most critical scientist would be that the methyl-cholanthrene had brought about in some mysterious way an intracellular change in the original cells, which confers upon the cells an inherited capacity for continued growth and multiplication—which is cancer. The easy acceptance of these negative findings has not appealed to us because of the fact that tumours transmissible with dry tissue do exist, and we have thought that previous failures were more likely to be a consequence of our ignorance of the correct technique than to new mysteries peculiar to cancer.

2. The second is a sarcoma of the pure strain of mice known as R III. This tumour was derived from the stroma of a transplant of a spontaneous mammary cancer in the same strain; it was separated from the original cancer by early transfers by Dr. Ludford. The sarcomatous elements grew much more rapidly than the carcinomatous tissue, and by grafting tumours whilst they were still small, the epithelial malignant cells were left behind in the race for survival and were lost. The tumour finally became the most malignant strain we possess; it consists of sarcoma cells of the most diverse shapes and sizes, from spindle cells to enormous multi-nucleated giant cells; some areas of the tumour contain masses of ruptured cells lying in a ropy mucous fluid.

Attempts had been made during the war period to propagate this tumour with cell-free extracts but all ended in failure.

3. A tumour similar to R III sarcoma but in another strain of mice, the C3H. This also was separated from a carcinoma by Dr. Ludford,

and though not perhaps so malignant as the R III sarcoma, is nevertheless of exceptional malignancy.

The usual technique of drying tumours consists in keeping minced tissue over phosphorus pentoxide *in vacuo* in the cold room (4° C.) for several days. When one of the filtrable tumours of the domestic fowl is dried in this way, and the scaly brownish residue is powdered in a dry mortar, the powder emulsified in distilled water and the emulsion then injected into the appropriate animal, a tumour forms at the site of the inoculation. Improved methods of drying have been devised by numerous workers in the U.S.A. and in England, but none of these gave positive results with any of the three mouse sarcomas under investigation. An improved pattern of drying apparatus was therefore designed by Dr. Craigie, one in which the tissues being dried are maintained at a temperature of -22° to -25° C. Details of the apparatus are now in the scientific press.

With this apparatus, which dries a gramme of finely divided tumour tissue in less than an hour, all attempts so far to obtain active dried material of freshly removed C 48 tumour tissue have failed. When, however, the finely minced tumour tissue, suspended in an equal volume of 5.3 per cent. glucose solution, has been kept five to seven weeks at a temperature of -79° C., is dried and an emulsion of dry dead cells injected, tumours form at the site of inoculation. In some experiments 80 per cent. of the mice yield tumours, which appear in 12 to 16 days; in others one tumour only out of ten mice injected; in others none. There is thus a variability in infectivity which is either in the "nature of things" or is due to some technical flaw not yet under control. But it should be stated quite clearly that tissues from this methyl-cholanthrene-induced tumour, kept five to seven weeks at the low temperature of solid carbon dioxide, have been dried to dust and have been proved to be active sufficiently often to warrant this report.

We arrive therefore at this situation: A tumour was started seven years ago by injecting a pure chemical carcinogen; during these seven years the tumour was successfully propagated with living cell grafts and numerous attempts to propagate it with dry tissue or with cell-free extracts had failed; when emulsified tumour tissue is kept at the very low temperature of -79° C. the tissue does not lose its power to give rise to a tumour when inoculated into suitable mice; indeed, this is a tumour which appears to be "improved" by keeping at very low temperatures; and now, although fresh tissue still fails to yield active dry residue, refrigerated tissue does.

The simplest working hypothesis of the origin of the tumour is one which has been entertained by a few cancer workers, namely, that the action of the pure chemical prepares cells in the area in which it is placed to accept a latent virus already in existence in the bodies of the normal mice. That such viruses do exist in a latent form has been proved for many viruses, including tumour viruses; Little and his collaborators, for

example, have proved that Bittner's mammary cancer virus is latent in the blood and tissues of male mice of a high cancer line. Hitherto, however, such opinions lacked the necessary factual backing.

This has now been provided, and this chemically induced tumour can be put in the same class as the sarcomas of birds or the papilloma of the cotton-tail rabbit.

A brief account of two drying experiments illustrates the kind of work which we are doing.

On August 3, 1948, three tumours of the strain C 48 were removed aseptically, minced finely, diluted with an equal volume of 5.3 per cent. solution of glucose, distributed in 2 c.c. lots in ampoules which were sealed and stored in a CO<sub>2</sub> ice refrigerator. The ampoules were kept at -79° C. untouched until September 24, that is for 52 days, when one was taken out, the tissue thawed rapidly and dried in Dr. Craigie's apparatus. Whilst the drying was proceeding, the small amount of tissue left in the ampoule was injected subcutaneously in four normal mice of the C 57 strain; all of these mice developed tumours rapidly and were killed 21 days later. The tissue for drying, approximately 1 gramme in 1 c.c. of 5.3 per cent. glucose, was completely dry in three hours; to it was then added 5 c.c. of a neutral solution of 1 in 500 cysteine. The suspension of dried tissue was immediately injected into 18 normal C 57 mice in approximately equal doses; tumours began to appear in 14 days. On October 25, 1948, 31 days after the experiment was started, there were 13 large tumours out of 18 mice. One of these tumours was minced finely on October 28, the mince mixed with glucose, distributed in ampoules and placed in the CO<sub>2</sub> refrigerator. On December 20, 1948, i.e., 53 days later, one of the ampoules was taken out of the refrigerator, the tissue suspension thawed and the experiment already described repeated. On this occasion 12 mice were injected with the suspension of dry tissue. At the time of writing there are nine tumours, of which one has been, in laboratory slang, "canned" and put away in the carbon dioxide refrigerator for repetition of the experiment.

Unlike the chemical tumour No. C 48, both the sarcomas R III and C3H, derived from breast cancers, have been transmitted with dried tissue of fresh tumour. In other words, it has not been necessary to subject the tumour tissue to a long period of storage at -79° C. before drying it. The short period at -25° C. to which it is subjected during desiccation is apparently sufficient to activate this highly malignant tumour to allow of its propagation by dried tissue. As has been suggested, the process of inbreeding for tumours possibly picks out strains of virus which are unstable, have a high mutation rate, and which are endowed with exceptional virulence.

The tumours which develop, following injection of dry tissues of these R III and C3H sarcomas, appear as a rule in 12 to 16 days, but sometimes, especially with the R 3 strain, they can be detected on the 8th day. The following is a brief account of an actual experiment.

On November 12, 1948, five R III sarcomas were taken and minced finely with Dr. Craigie's mincer. To the 5 c.c. of mince thus obtained, 2 c.c. of 5.3 per cent. solution of glucose was added. This dispersion of sarcoma cells was distributed in ampoules, 2 c.c. in each of three, 1 c.c. in a fourth ampoule; the ampoules were sealed and stored at  $-79^{\circ}\text{C}$ .

On December 16, 1948, 34 days later, one ampoule containing 2 c.c. of dispersed sarcoma cells, was opened, 1 c.c. of 5.3 per cent. glucose solution added, and the final mixture of 3 c.c. was dried. Drying was complete in 110 minutes but the machine was allowed to run for a further 20 minutes.

The fine dry scales of tissue and glucose were mixed with 3 c.c. of 1 in a 1,000 solution of cysteine of pH 7.5. This suspension was immediately injected in 0.3 c.c. doses into 10 normal R III mice. Eight days later small tumours were detected at the site of inoculation. On the 13th day after inoculation all the mice had large tumours.

On January 3, 1949, three of the tumours induced with dry tissue were removed aseptically, minced and suspended in an equal volume of 5.3 per cent. glucose solution. The volume of the minced tissue was 3 c.c., of the glucose solution 3 c.c.; 2 c.c. of the suspension of cells was dried at once and the dry residue, suspended in 1 in 1,000 neutral cysteine solution, injected in 10 normal mice. Fifteen days later seven of the mice had large tumours.

The sarcoma of C3H mice likewise has yielded very active dry residue; further description is mere duplication.

Each of the three tumours transmitted with dry tissue has characteristic naked-eye and microscopic appearances. These are perfectly reproduced in the tumours obtained by non-cellular transmission. In this respect they resemble the fowl sarcomas described so completely by Peyton Rous.

In the wide search for tumours of many species of animals, a few tumours, naturally and readily filtrable, have been come upon accidentally. It is possible, indeed probable, that naturally filtrable tumours of mammals will be found; Shope's discovery of the virus-papilloma of the American wild rabbit is a warrant for this prophecy. But the tumours which have been used in this work are tumours of every-day experience of all cancer research laboratories and have hitherto resisted non-cellular propagation. Moreover, so far as the chemically induced tumour is concerned, it has so far proved to be necessary to keep the tumour at a low temperature for some weeks to get active dried tissue. It seems to us these results warrant us drawing the following conclusions.

The apparent gap between filtrable and non-filtrable tumours is fictitious; the difference between chicken tumours and mammalian tumours is quantitative and not qualitative. Even the violent tumour known as the Rous sarcoma is sometimes non-filtrable and dry tissues of the tumour in this phase of its growth are inactive. Tumours of small mammals normally yield inactive dry tissue; by the techniques briefly described in this Report active dry tissue can be obtained. Doubtless

more and deeper knowledge and possibly new methods of experimentation will be needed to obtain active dry tissue from other tumours ; indeed, work which is in progress appears to indicate that cell and nuclear membranes play a part in allowing or resisting the freeing of virus. Further, since it has been proved that the virus of the tumours already successfully transferred without living cells is very unstable, it will be essential to discover methods of preserving virus at room temperatures. But all this belongs to the future. It is sufficient to say that the negative results obtained hitherto in attempts to achieve non-cellular propagation of tumours mean precisely that the methods were not good enough for the task and that they do not warrant either the pessimism of the past or the rather wild popular speculations of the present. If, as is almost certain, low temperatures kill the delicate mammalian cell but do not affect the virus, which is what might be supposed on our present knowledge of cells and viruses, then we have no need for further proof that viruses are the continuing cause of cancer than is provided by Ehrlich's famous experiment which has already been referred to.\*

### NATURAL HISTORY OF CANCER BITTNER'S MAMMARY CANCER VIRUS

Three papers dealing with the occurrence and growth of mammary tumours in hybrid mice have been prepared for publication by Dr. Foulds. As recorded, briefly, in the last Annual Report, mammary tumours were found in female hybrid mice having mothers of the inbred strain C 57 Black which is almost exempt from mammary cancer, and fathers of the strain C3H which has a high incidence of mammary cancer. Some of the tumours, although in other respects indistinguishable from the familiar mammary tumours of mice, grew when transplanted into female mice of appropriate genetic constitution, but they did not grow in male mice unless an œstrogen was administered. These observations prompted the study of two main problems ; first, the contribution of the mammary tumour agent or "milk factor" to the production of the tumours of hybrid mice and, secondly, the regulation of tumour growth by hormones.

According to the widely accepted view of Bittner, three factors co-operate to evoke mammary tumours in mice : a genetic factor, a hormonal factor, and a mammary tumour agent or "milk factor" which is transmitted from mother to offspring in the milk. The occurrence, against expectation, of variable though sometimes substantial numbers of tumours in hybrid mice suckled by low-cancer strain mothers presumed deficient in the tumour agent has been variously, but not satisfactorily, explained. The explanations were in the main speculative, because it was not proved whether or not the hybrid mice and their tumours carried the tumour agent. It has now been shown, by direct test, that a transplantable tumour obtained from a hybrid mouse with a C 57 Black mother and an

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\* Since this report was written Miss Mann has succeeded in propagating a sporadic carcinoma with dried tissue.

R III father contains the tumour agent. Furthermore, breeding experiments provided indirect evidence for the presence of tumour agent in some of the hybrids. The progeny of two tumour-bearing hybrid mice developed mammary tumours abundantly, the incidence being about 70 per cent. By contrast the progeny of a similar hybrid female which was free from mammary cancer when killed at an advanced age, rarely developed mammary tumours; the incidence in three generations ranging from 0 to 3 per cent. The first generation hybrids, therefore, although genetically alike, differed amongst themselves. A minority of the hybrid females developed mammary tumours, carried the tumour agent and transmitted the agent to their offspring, which behaved like mice of a "high-cancer" strain; the majority of the hybrid females did not develop mammary tumours and did not transmit tumour agent to their offspring, which behaved like mice of a "low-cancer" strain. In an experiment not yet complete, hybrid mice were obtained by mating C 57 Black females with males from a strain of R III which was raised by Dr. Pullinger and which lacks the tumour agent. Of 50 hybrid females over a year old, only one carries a possible mammary cancer. The low or moderate incidence of mammary tumours in hybrid mice having low-tumour strain mothers and high-tumour strain fathers, therefore, is attributed provisionally to erratic transmission of tumour virus by the male parents.

Other investigations were concerned not with the origin of tumours but with their behaviour after they were clinically apparent and, in particular, with their responsiveness to hormones. Transplanted tumours were first studied and subsequently more decisive observations were made on spontaneous tumours. It was shown that the dependence of certain tumours upon sex hormones for successful transplantation to new hosts was not correlated with presence or absence of the mammary tumour agent, and that the action of hormones was not restricted to the early stage of establishment of the tumours in new hosts. Hormones stimulated gross milky secretion in some transplanted tumours. Gross secretion was apparent only in tumours growing in pregnant females and in oestrogenized males; it disappeared from the males when the oestrogen was withdrawn. Some other transplanted tumours grew during pregnancy in female hosts and declined after parturition; most transplanted mammary tumours of mice, if they respond at all, are inhibited by pregnancy. The two responses to hormonal stimulation, by secretion and by accelerated growth, were independent of each other and each was manifest in only a minority of those transplanted tumours whose growth was inhibited in normal male hosts. The hormone responses depended on specific properties of individual tumours. The specific properties however, were not immutable; after repeated transplantations, secretion was no longer apparent and transplanted tumours grew equally in male and female hosts. Observations on spontaneous tumours, developing naturally in their original hosts, showed decisively that hormone

responsiveness was independent of the artificial conditions of transplantation.

The breeding experiments already mentioned yielded an abundant supply of spontaneous mammary tumours. Mice were examined regularly from the first appearance of a tumour until death, when the majority had multiple tumours. Each tumour was measured repeatedly and its growth was plotted graphically. The graphs of several hundred tumours revealed great diversity of behaviour, accountable, however, to two or three main factors. Some tumours grew steadily and progressively from their first clinical appearance until the death of their hosts; their course was represented graphically by an almost straight line. Other tumours were conspicuously different. Discovered as a rule during pregnancy, they grew to a peak near the time of parturition and thereafter regressed completely or partially, but recurred in the same position during the next pregnancy. Many tumours repeated these cycles of growth and regression in several successive pregnancies; their courses were represented graphically by wavy lines, with peaks sometimes at the same level and sometimes ascending, slowly or rapidly, in successive pregnancies. These tumours were designated "responsive" tumours, to distinguish them from the "unresponsive" tumours which grew steadily and progressively without deflection during pregnancy, or the puerperium. The responsive tumours were regulated, presumably, by hormonal stimuli, but the mechanism has not yet been elucidated; preliminary experiments indicate that simple oestrogenic stimulation is not sufficient to ensure growth.

The primary distinction was between responsive and unresponsive tumours, although transitional types were encountered. Within these main groups, further diversity was attributable to the interplay of factors which within wide limits were independent of each other. Responsiveness to pregnancy varied greatly in degree from one tumour to another and the rate of net growth, designated the "intrinsic growth rate," was similarly varied. A high degree of responsiveness to pregnancy might be associated with a low intrinsic growth rate or vice versa. Responsiveness to pregnancy and intrinsic growth rates were thus independent variables and varied combinations of the two properties accounted, in the main, for the observed diversity of behaviour of the tumours.

The degree of responsiveness to pregnancy and the intrinsic growth rate were specific properties which remained constant for a particular tumour, sometimes throughout its clinical course. Many tumours, however, changed their course during the period of observation. The repeated observation of a change in behaviour in one of two or three tumours present at the same time in the same mouse showed that the change was in the tumour itself and not in the environmental factors to which all the tumours were exposed. The altered behaviour resulted from an irreversible qualitative change, for which the term "Progression" is proposed by Dr. Foulds. Progression was manifested in either the



responsiveness or in the intrinsic growth rate. It was shown most conspicuously by an abrupt acceleration of the growth of unresponsive tumours and by the change, also apparently abrupt, of a strongly responsive tumour into a completely unresponsive tumour which grew steadily and progressively for the remainder of its course. Changes of less degree and of more gradual manifestation were also observed. Several tumours present in the same mouse at the same time sometimes behaved alike and sometimes differently, and the same tumour might behave differently at different times ; a true picture of the behaviour of mammary tumours could be obtained therefore, only by following every tumour through the whole of its course.

The most important outcome of these investigations was the elucidation of Progression as an important phenomenon in the natural history of tumours. The detailed analysis of the observations provided the basis for generalization or rules of progression which are here briefly summarized.

1. Progression occurred independently, and unpredictably, in multiple tumours in the same animal, irrespective of the size or clinical duration of the tumours. This we call the rule of *independent progression of multiple tumours*.
2. Progression affected separately the several recognizable characters of individual tumours as, for example, responsiveness and intrinsic growth rate. Rule of *independent progression of characters*.
3. Progression was *independent of growth* ; it occurred in stationary tumours and, apparently, in responsive tumours which had regressed, after parturition, beyond the limits of clinical recognition. Progression was often disclosed by the behaviour of a tumour at the end of pregnancy, but pregnancy was not the sole or essential cause, for progression was manifested sometimes during intermissions of breeding, when growth was in abeyance and, in general, in only one of several tumours exposed to the same pregnancies. The rule of progression independently of growth had two notable corollaries :—
  - (a) At its first clinical manifestation a tumour might be at any stage of progression.
  - (b) Progression was independent of the size or clinical duration of a tumour.
4. Progression might be continuous or discontinuous ; it advanced a tumour along one of alternative paths of development, and it did not always reach an end-point within the life-time of the host, further progression taking place after transplantation.

It is believed that these principles are widely applicable to the behaviour of tumours in animals and in man. In particular they account for many vagaries which have for long puzzled clinicians and pathologists. A few applications are here outlined.

## THE RESTORATION AND DEVELOPMENT FUND

The behaviour of tumours is the resultant of several characters which vary, within wide limits, independently of each other and undergo independent progression. The characters include growth rate, invasiveness, capacity for dissemination, and responsiveness to environmental stimuli, of which the hormones are the most easily recognized, but not necessarily the only, examples. "Malignancy" is not a single character. The typical malignant tumour of the text-books is the result of proportionate development of all the characters proper to malignant tumours. Independent progression of characters, however, results in disproportionate or "out-of-step" development as, for example, in the "benign" tumours which metastasize and the "locally malignant" tumours which do not. This out-of-step development is especially important in cancer of the prostate which, despite conspicuous growth, invasion and dissemination, is responsive to ovarian hormones.

Errors in the prognosis of "early" tumours are explained by the rule that progression occurs without manifest growth and independently of the size or duration of a tumour. A tumour may be small in size and young in clinical duration but far advanced in the progression of aggressive characters. Progression without manifest growth and independent of size and duration probably accounts, too, for the otherwise mysterious but clinically important phenomena of long-delayed recurrences and secondary growths after apparent cure of a primary tumour. The ultimate failure of several chemotherapeutic methods after favourable immediate response is reasonably attributed to progression in the inhibited tumours; in mice the onset of unresponsive, progressive growth in hitherto responsive mammary tumours whose growth has been inhibited by interruption of breeding provides an impressive analogy. Further elucidation of progression, especially the independent progression of characters and progression when growth is inhibited, is evidently of prime importance for the management of human cancer.

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## THE RESTORATION AND DEVELOPMENT FUND

RECENT GIFTS to the Restoration and Development Fund include two hundred guineas from Mr. Edward C. Bell Jones, of Ipswich, and two hundred pounds from Mr. H. J. Joel, a generous supporter of the College who, as Fellows will remember, presented a Rowlandson drawing of John Heaviside delivering a lecture in the theatre of the Company of Surgeons.

# NON-UNION OF FRACTURES OF THE MANDIBLE

Lecture delivered at the Royal College of Surgeons of England  
on

9th March, 1949

by

Rainsford Mowlem, F.R.C.S.

Surgeon-in-Charge Plastic Department, The Middlesex Hospital

WITHIN A FEW HOURS of the receipt of a fracture the processes of repair have commenced. The various phases should proceed without interruption to reach completion in a matter of weeks, but, particularly in the earlier stages, even minor disturbances may check or halt the orderly sequence of regeneration. The most important of the many possible causes of non-union are mechanical trauma and infection. Both of these are most likely to interfere with bone regeneration in the earlier rather than in the later stages and their avoidance is a matter of urgency. Either singly or together these factors will be found to be at the root of most of the accepted causes of non-union which will be dealt with later, and it is only by a clear appreciation of their importance that effective measures to avoid their occurrence can be instituted sufficiently early to eliminate them completely.

Efficient treatment of a simple fracture should result in clinical union between the bone ends within six to eight weeks. This period may be decreased very considerably in the young and may be increased by other factors, so that there is no arbitrary end point at which one can say that a given fracture will never unite spontaneously and that non-union must therefore be assumed. Nevertheless, in most fractures clinical evidence of bony union should be obvious in less than two months.

The criterion of union is essentially clinical and not radiographic. After the sixth week the fracture line should feel firm though absolute rigidity may not be present. The only movement which can sometimes be elicited in a fracture which is progressing satisfactorily is a very slight non-elastic angulation at the fracture line and this usually disappears within 7 to 14 days after removal of the splint fixation. So long as it is present it may be wise to retain the splintage in position although it should not be locked.

X-ray examination may produce many misleading diagnoses and it has, before now, been responsible for the reference of cases for active surgical intervention to cure a fracture which has, in fact, already firmly united.

Figs. 1—5 are the X-rays of a simple fracture treated and recorded by Dr. Alexander MacGregor. At no stage was splintage necessary or desirable and at no time was the patient, a serving officer, off duty. He was, from the clinical point of view, unaware of the presence of his fracture, and yet it will be seen that six months elapsed before the X-rays showed bony continuity in the jaw.



Fig. 1. Inverted Y-shaped fracture through the body of the mandible with no displacement and no mobility. No treatment was necessary.



Fig. 2. The X-ray appearances at three weeks.



Fig. 3. The X-ray appearances at 10 weeks.



Fig. 4. The X-ray appearances at 17 weeks. At this stage it was reported that there was probably a sequestrum in the fracture line but there was no clinical evidence of infection.

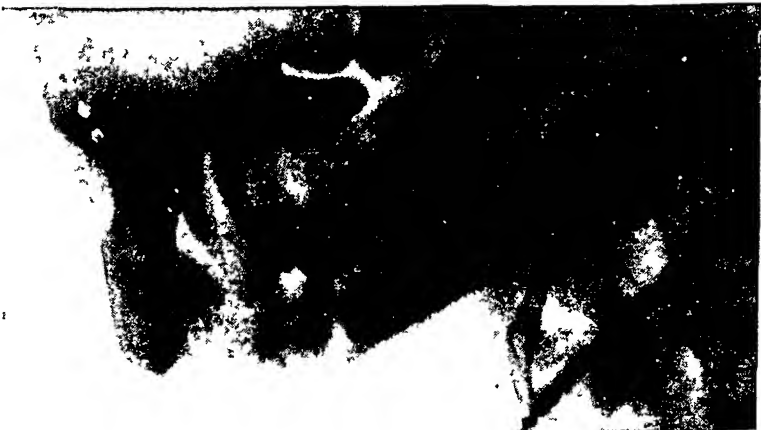


Fig. 5. X-ray appearances at 30 weeks. Even at this date complete bone continuity is not restored.

Under ideal conditions any fracture should be immediately reduced to restore perfection of alignment; it should be efficiently maintained in this position until new bone has bridged the defect and it should at all stages be protected against infection. These desiderata are not always capable of complete realisation, and in the different parts of the mandible differing problems and behaviour can be anticipated.

(1) *Condyle and neck*.—In many fractures in this region no fixation is required because the patient can reach and maintain normal dental occlusion. The fracture therefore may never be splinted, but in spite of this the great majority appear to unite even though the alignment be bad. It seems probable that this is due to the fact that the condylar displacement is most frequently an angulation which leaves the fractured ends in fairly close approximation. In addition to this, the periosteum and the fibres of the capsule of the temporo-mandibular joint remain, at least in part, as a sufficient fixation between the bone ends. The possibility of infection, except in the rare penetrating injuries, does not exist to complicate the issue.

(2) *Angle and ascending ramus*.—In this part of the mandible the bone is clothed on both surfaces by bulky muscles and their presence may be either a cause of difficulties or a source of protection. In some oblique fractures, no bony mechanical barrier remains to resist the pull of the temporalis and the internal pterygoid muscles. As a result the posterior fragment is adducted and flexed, and this displacement may be of such a degree that the defect between the bone ends becomes too great for bone regeneration to cross it. Adequate reduction and splintage of the fracture line is the primary necessity and it is in this area that the relatively new methods of cross pin or screw fixation have been so successful. It must however be appreciated that the power of the muscles which cause the displacement is very great and the comparatively frail pins which were first advocated have been found inadequate. Heavy pins at least  $\frac{1}{8}$  in. in diameter with correspondingly heavy external bars are very necessary if reduction is to be maintained. When, however, a satisfactory realignment is obtained, union is usually speedy.

In other types of fracture in this region the lines of the break lie in such a plane as to offer resistance to the muscular pull and no displacement occurs. All that is then necessary is splintage of the main body of the mandible to the maxilla, and when this is obtained the fracture lines, clothed as they are by vascular muscle tissue, will unite rapidly and without complications.

(3) *Body and symphysis*.—It is in this area that non-union can most readily occur. Mechanical trauma of the unsplinted fracture is likely to be excessive because all the flexors of the mandible lie posterior to the fracture line. The anterior fragment has attached the muscles of the floor of the mouth and the suprahyoid group and though these are relatively weak they are markedly assisted by gravity. Any attempt on

the patient's part to move the jaw or even to swallow may well produce a shearing action across the fracture line. This movement has two results. Firstly it may actually interfere with the early stages of new bone formation and secondly by alternately opening and closing the fracture line it will tend to aspirate infected debris from within the mouth into the space between the bone ends. Such an uncontrolled combination of trauma and infection lays the foundation of *non-union*.

In any fracture in the body therefore the potential causes of trouble may be present and it is the urgent duty of the surgeon to see that they are brought under control at the earliest possible moment.

The important factors which can convert the potential risks into real dangers are as follows :

(1) *Delay in fixation*.—With every hour that elapses between the incidence of a fracture and its adequate splintage the mouth tends to become more foul. Debris and dried mucus collects because of the protective immobility of the tongue and the jaw. The self cleansing apparatus is out of action and bacterial contamination increases.

At the same time each attempted movement of swallowing inflicts mechanical damage on the bone ends and, ensures that the contents of the infected mouth are effectively brought into contact with them.

Efficient fixation—even though it may be temporary—is an urgent essential.

(2) *Inadequate reduction*.—Failure to obtain reduction and fixation is probably most often due to a choice of the wrong methods, but there are two conditions other than this which may present themselves.

(a) Towards the angle, muscle fibres of the masseter or the internal pterygoid may come to lie between the bone ends. Reduction is impossible and non-union will result. At the time of attempted reduction the cushioning effect of the interposed muscles should be apparent and an X-ray will reveal a substantial space between the bone ends. The remedy obviously lies in open operation.

(b) It is not uncommon to encounter a fracture line in the form of an inverted Y, e.g. (Fig. 1). The triangular fragment may be very large and may tend to be displaced downward. If the presence of this fragment is not appreciated it may be that, even after the restoration of perfect dental alignment, the mandible will be in contact only over a small area in the alveolar region. Beneath this point there is a large space filled with blood clot and lying lower still is the bone fragment. The amount of alveolar contact may be insufficient to allow of the regeneration of a firm bony bridge and there is the not inconsiderable risk of infection in the large dead space which should be occupied by the displaced triangular segment of lower border. Difficulties of this nature can be avoided by adequate X-rays and by providing for fixation of all major fragments which take part in an irregular fracture line. In the case stated a probable solution would lie in the use of cap splints to restore the line of the *mandibular arch together with a circumferential wire passing beneath*

the displaced fragment and anchoring it back into contact with both mandibular ends. Similar difficulties may arise in the markedly oblique fractures which are sometimes seen commencing near the mid line and extending backwards and downwards into the floor of the mouth.

(3) *Inefficient fixation*.—Although satisfactory reduction may have been obtained, check X-rays may reveal some recurrence of the displacement. Alternatively it may be that the splintage is inefficient in eliminating movement between the bone ends. Such a state of affairs is almost certainly due either to the choice of the wrong method of fixation or to the utilization of appliances which are too light to withstand the not inconsiderable stresses to which they will be subjected. It is usually preferable to review the whole problem rather than to wait from day to day to evaluate the result. The later in the cycle of bone regeneration any major manipulations are carried out, the greater is the check to speedy union.

(4) *Teeth or tooth remnants in the fracture line*.—There has been a tendency to assume that teeth standing in the fracture line are an important cause of non-union. This appears to be an over-statement.

In spite of X-ray appearances many fracture lines tend to pass between the teeth without exposing them and there is no reason to suppose that the presence of these teeth will in any way interfere with bone regeneration. Even when the root of a tooth is exposed very satisfactory union can usually be expected, provided that the tooth as a whole retains firm attachment to the mandible. The presence of such a tooth, especially if it be a seven or an eight, may so simplify fixation as to justify its retention even if it must ultimately be sacrificed.

Whenever a tooth is firm but partially exposed it is, however, desirable to exclude it from the fixation so that it may later be removed if it becomes necessary. Less interference with bone growth may well result from such a policy than from the carrying out of a difficult extraction from the mobile end of a recently fractured jaw.

If, however, a tooth or part of a tooth has been dislodged and devitalized and lies as a foreign body in the fracture line, its immediate removal is imperative (Figs. 6, 7, 8, 9), as otherwise it becomes the site of an infection which may well cause non-union.

(5) *Gross comminution of the mandible*.—This condition is most frequently caused by penetrating injuries. The fracture, therefore, is compound both internally and externally. With conservative treatment a few cases may achieve union after a long period characterized by repeated sequestrectomy and drainage. It would appear much more reasonable to accept the fact that non-union is the probable end result—to splint the main mandibular fragments in their correct position, to open the fracture area widely and to remove all devitalized bone and close the defect in the oral mucous membrane (Figs. 10, 11, 12, 13). Infection should be eliminated and within a comparatively short time surgical reconstruction of the defect can be carried out.





Fig. 6. Fracture involving the tooth root. Note the temporary intermaxillary fixation.



Fig. 7. The crown of the tooth has been removed but its anterior root remains in the fracture line and infection is obvious round it.

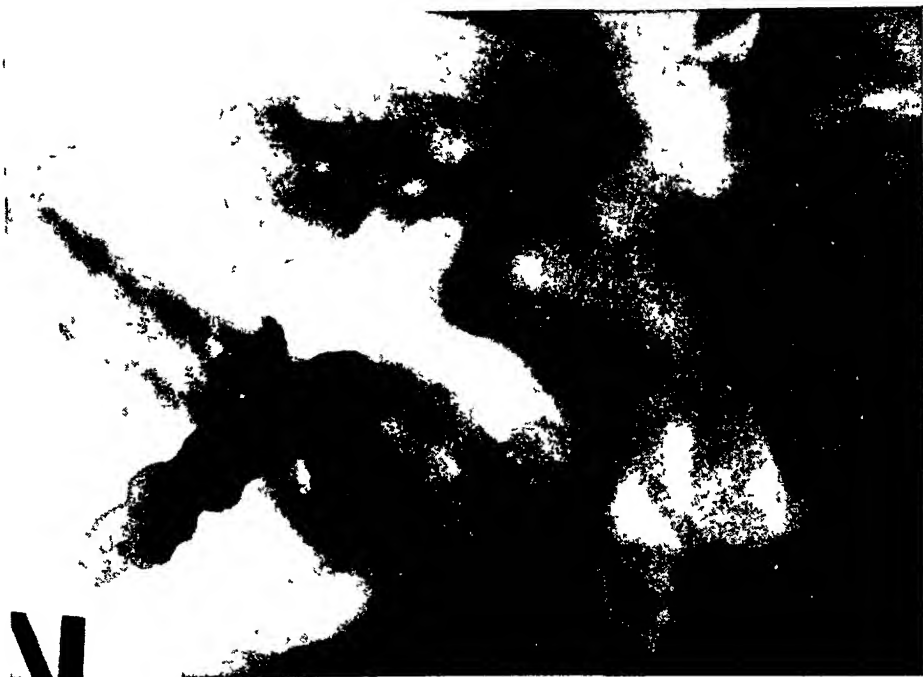


Fig. 8. Permanent splintage has been applied, the affected tooth root and dead bone removed.

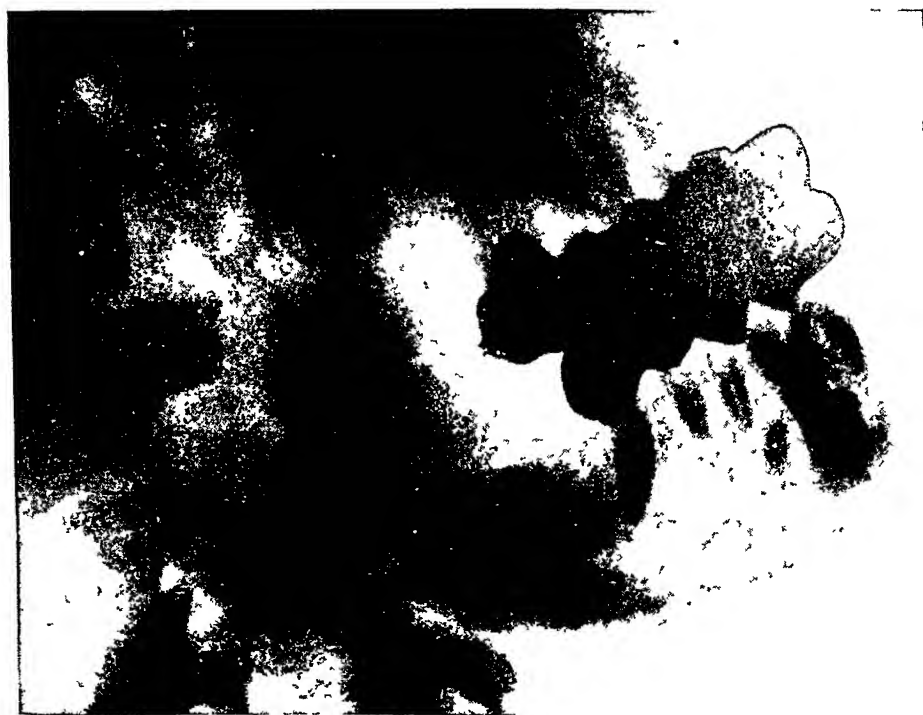


Fig. 9. Satisfactory regeneration occurring.



Fig. 10. A compound comminuted fracture some days old. No fixation has yet been applied.



Fig. 11. Same fracture after application of the fixation.



Fig. 12. Through an external approach all dead bone has been cleared out leaving a wide gap.



Fig. 13. Established non-union immediately prior to bone grafting.

## TREATMENT OF NON-UNION

(1) *Expectant*.—Treatment has already been dealt with under the headings given above and it is obvious that every endeavour should be made from the first day to eliminate all possible causes of non-union. If, however, in spite of this the fracture is not united in six to eight weeks active measures should be taken.

(2) *Reparative*.—The older method of closing the gap by approximation of the bone ends irrespective of mal occlusion has now, in the great majority of cases, been abandoned and the present method is by bone grafting as soon as it is obvious that the condition is established.

## PRE-REQUISITES FOR BONE GRAFTING

(a) The sound closure of all fistulæ into the mouth so as to allow of adequate dissection of the mucous membrane from the bone ends without perforation.

(b) The elimination of all evidences of external infection and fibrosis. A period of six to eight weeks should be allowed to elapse from the time when any external wound becomes dry until the time of bone grafting. This delay is of more value in allowing resorption of deep fibrosis in the soft tissues than in ensuring that a recrudescence of infection from the bone ends does not occur.

(c) It is usually advantageous to have no teeth within about  $\frac{3}{8}$  in. of the bone ends. The reason for this is that the bone ends are cut back to produce a vascular surface and it is undesirable to expose a tooth root during this process.

(d) The provision of adequate fixation to retain both fragments of the mandible in their correct "bite" relationship after operation. It may be that in some cases normal occlusion cannot be obtained until the bone ends have been freed from each other. Under these circumstances the construction of the final locking mechanism will be carried out actually during operation.

*Operation*.—All fixation appliances are unlocked before operation to avoid displacing splints.

Access to the bone ends is obtained through an incision just below the lower margin of the mandible. The incision is deepened to the fragments, from which the periosteum is stripped on the lower margin and the buccal aspect. The scar tissue between the fragments is removed with care to avoid entering the mouth. The dissection is continued up to the alveolar margin of each fragment and then extends down the whole of the lingual aspect for an antero-posterior distance of about  $\frac{1}{2}$  in. All eburnated bone is cut away from the bone ends and a wedge of the outer aspect of each fragment is removed to create a large vascular surface with which the bone graft can make contact.

When this stage is complete the mandibular fragments are fixed in their correct alignment either by some pre-arranged method, or by a

locking device made at this stage. If the operation has been commenced with fixed splintage in position dissection is rendered more difficult and there is every chance of dislodging the splints.

When satisfactory realignment has been established the defect between the bone ends is bridged by the bone graft. In some instances this may be a solid graft, but more frequently it consists of cancellous chips which are derived from the iliac crest. A thin plate of cancellous bone is placed lingually to the bone ends. This serves to prevent movements of the muscles of the floor of the mouth from being transmitted to the overlying cancellous chips which are placed between the bone ends. A satisfactory contour is built up and the chips are retained in position only by suture of the subcutaneous tissues over them. The skin is closed as a separate layer.

The splintage remains in position for from four to five weeks. At the end of this time the graft is tested for clinical rigidity and if satisfactory all splints are discarded.

When it is appreciated that the average period of splintage for a bone graft is as short as this, it will be realised that whenever non-union is a probability it may be preferable to concentrate on preparing the patient for grafting rather than condemning him to an indeterminate period of splint fixation without any real guarantee that solid regeneration will be the ultimate outcome.

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## THE JOSEPH HENRY LECTURESHIP

DR. S. A. HENRY, F.R.C.P., M.R.C.S., late H.M. Inspector of Factories, has founded a lectureship in Occupational Surgery, or surgery in relation to occupations especially industrial, in memory of his father, Dr. Joseph Henry.

Dr. Henry and his sister, Miss Mabel Henry, have inaugurated the endowment fund by generous donations of £300 each. The conditions of the award of the lectureship will be determined in consultation with the donors.

## CONFERRING OF THE HONORARY FELLOWSHIP ON VISCOUNT NUFFIELD

Speech by the President, Lord Webb-Johnson.

“ LADIES AND GENTLEMEN, it is nigh on seven years since we invited Lord Nuffield to our College in order to show our appreciation of his tremendous services to British Medicine. On that occasion we conferred on him the Honorary Medal of the College, our most exclusive emblem of merit. It had then been founded for 140 years, and Lord Nuffield was only the nineteenth recipient. His particular medal is *primus inter pares* for it is the only one that has been cast in bronze. The award was made in war time, when the use of gold was forbidden, but, as I remarked when making the presentation, ‘When Britain is at war how much richer than red gold this dull bronze seems!’

On the previous occasion our desire was to do honour to Lord Nuffield because of his remarkable gifts to British Medicine. To-day the case is different. Lord Nuffield has made a gift which will provide in our College facilities and amenities which will be absolutely unique in the world. So, to-day, we invite Lord Nuffield to become one of ourselves—an Honorary Fellow of our College—one of our Corporate body.

Seven years ago there was assembled in this room a company representative of all branches of British Medicine, and of all Estates of the Realm. To-day the theatre is filled with keen graduate students from this country and from all parts of the Commonwealth—by men and women who know what Lord Nuffield’s gift will mean to those who follow them in the succession of students who come to London seeking advanced teaching in surgery and the basic surgical sciences.

Lord Nuffield knew that London could provide for post-graduate medical students a wealth of opportunity that could not be surpassed, but he saw that there was one thing lacking if aspirants to high places in surgery were to get the most out of their sojourn in London. They needed a Residential College in the precincts of their academic headquarters. Lord Nuffield’s gift will provide such a College, and those who have the privilege of residence will be able not only to have free access at all times to our unique museums, and to the library and the laboratories, but also to live together, and meet socially the principal surgeons of this country and distinguished teachers from other countries who may be visiting London. Thus they will absorb something of the spirit of the collegiate life of our older residential universities, and they will make contacts with leaders of their profession which will be a stimulus to them and their pupils throughout their lives, however many thousands of miles away from London they may be.

Let me give you an example by telling you what might have been! If such a College had existed in my young graduate days I might have sat next to the immortal Lister. What a precious life-long memory!!”

MR. L. E. C. NORBURY, Senior Vice-President, in presenting Viscount Nuffield, said : " My Lord President, I have the honour to present to you William Richard, Viscount Nuffield, to receive at your hands the Honorary Fellowship of this College. As you have said, this is not the first occasion on which the College has had the privilege to honour Lord Nuffield. The name of Nuffield stands for generosity and progress, and by his generosity in many fields, and on many diverse occasions he has made progress possible. The establishment of Residential Quarters in the College, for post-graduate students has been a dream of yours, My Lord President, and for some years you have realised the importance of a collegiate life for post-graduate students. Lord Nuffield has turned your dream into a reality with the magnificent gift of the Nuffield College of Surgical Sciences. He, too, realised the importance of providing residential accommodation for graduates within the precincts of the College. As a forerunner of things to come, and in order to meet the need at once, the Council has provided a temporary Residential College which Lord Nuffield has kindly consented to declare open to-day. The present students and the generations to come will bless the name of Nuffield. They are deeply conscious of all that he has done, and is doing in the cause of science and education."

THE PRESIDENT then handed the Diploma to Lord Nuffield with the words : " In the name of the College and by the authority of the Council I admit you as a Fellow of the Royal College of Surgeons of England—*honoris causa*."

VISCOUNT NUFFIELD replied : " My Lord President, Ladies and Gentlemen, I am not going to make a speech. I want, however, to thank you for the honour you have done me, and I am sure you will realise how much I appreciate it. When I was young I wanted to be a surgeon, but there was no money to become a surgeon with : so I have had to wait until this great day when I have become a Fellow of this famous College."

At the luncheon which followed Lord Nuffield's health was proposed by two of the graduates in residence in the College :

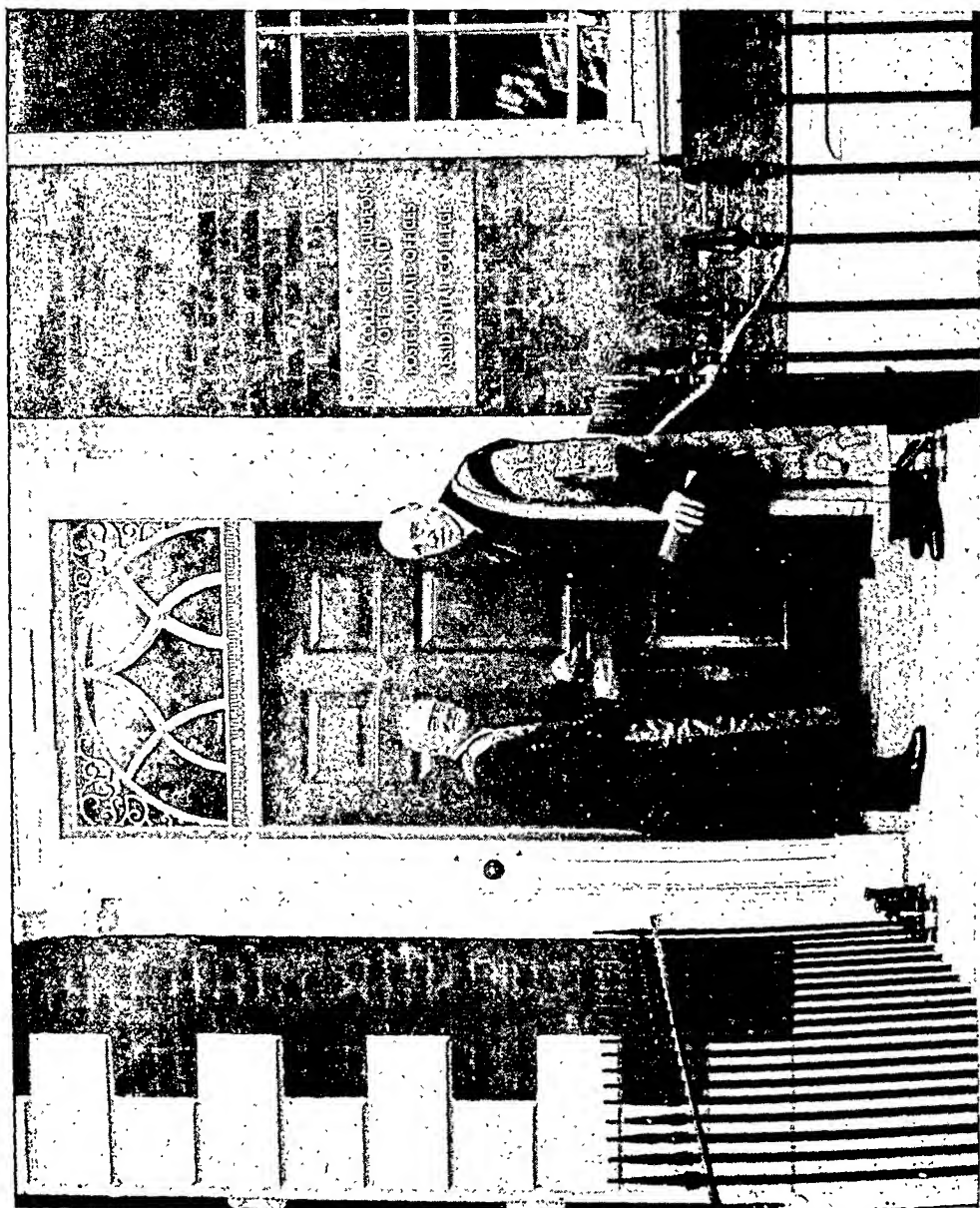
MR. TEMPLE BROWN, of Newton Abbott, said : " My Lord President, Viscount Nuffield, Ladies and Gentlemen, Ten years ago we were all tumbled unceremoniously into the crucible of a war that spared none, and, as the temperature rose, we all received a very uncomfortable handling, but I believe that the refining process was not entirely disastrous.

Although so much was burned away so quickly there still remain the indestructible human characteristics of courage, vision, enterprise and faith.

Although, to our great sorrow, much of the cherished and irreplaceable Hunterian collection perished in the flames, it left us in the ruins a challenge to start again.

Thanks to the vision of our guest of honour to-day that challenge has been met, and a new centre of surgical enterprise is to arise in this ancient





By kind permission of *The Times*

Viscount Nuffield opening the temporary Residential College with the President, Lord Webb-Johnson.

College, which will be equipped with a College of Residence as an integral part of its buildings. The first residents have a warm appreciation of Lord Nuffield's generosity, of which we would like him to be aware. It is my great delight, as one of the first residents, to express our gratitude for the singular advantages we enjoy—the day-to-day contacts and opportunities for friendships with men of a common interest from all parts of the world, and the sense of community peculiar to collegiate life. These are the attributes of our traditional centres of culture. Their value is enormous and we all enjoy them keenly.

Playing different parts in the deadly conflict recently over, many of us had to postpone our personal ambitions to a more opportune moment, but now that we are privileged to follow our individual stars in the intensely stimulating atmosphere of this Residential College, we may certainly feel that it has been well worth while to wait for this unique event in our lives, this unforgettable experience for which we are so deeply grateful to Lord Nuffield."

MR. S. R. TAITZ, of South Africa, said: "No one coming from the Dominions needs to be told of the great interest Lord Nuffield takes in the advancement of surgery. In every hospital in South Africa and in the other Dominions we have tangible evidence in the Nuffield respirators, in the Nuffield Scholarships and so on. I venture to suggest that his latest step in founding the Nuffield College of Surgical Sciences and the Residential College will have important repercussions on the future of surgery, not only in this country but in the Dominions and in other countries whose surgeons will be fortunate to come and stay in this important headquarters of surgery.

We, the first residents of this College, not only from the United Kingdom, but from the Dominions and from countries outside the Commonwealth can appreciate the privilege of living in the College.

The material benefits—the availability of the library, the museums, and the laboratories, the comfortable quarters and the helpful staff—are themselves great. But more important still is the fact that we now have a place where we can meet and discuss advances and problems in surgery among ourselves and with the leaders in surgical thought away from the lecture rooms and formal meetings.

Most of our traditions in surgery in the new countries of the Commonwealth have been brought to us from here, and now we have the privilege of living at the fountain head of these traditions in the Royal College of Surgeons of England, where all are imbued with the history and traditions of the College.

Most of us are preparing for the examinations of this College, but another important function of the residence is that of providing accommodation for those established surgeons who come to London to see the latest advances in the science and art of surgery.

These fortunate people, untroubled by the fear of the Court of Examiners, gain much from the facilities provided for them by the

College, but also give to the College and to the other residents the benefit, in free discussion, of their experience in the practice of surgery in the various countries which make up the Commonwealth. We also have the opportunities here of finding out more about each other and about life in general in countries both in the Commonwealth and outside it.

This ancient College which has always been in the forefront of surgical thought and progress, and has served as a model for other surgical foundations, now still leads in this new venture for which we are exceedingly grateful and is the envy of our colleagues at home, and those here working in other branches of medicine.

Speaking for myself and for the other overseas students, I can assure you that the profound influence which this College has always exerted in the art and science of surgery will be greatly intensified by this new activity made possible by Lord Nuffield."

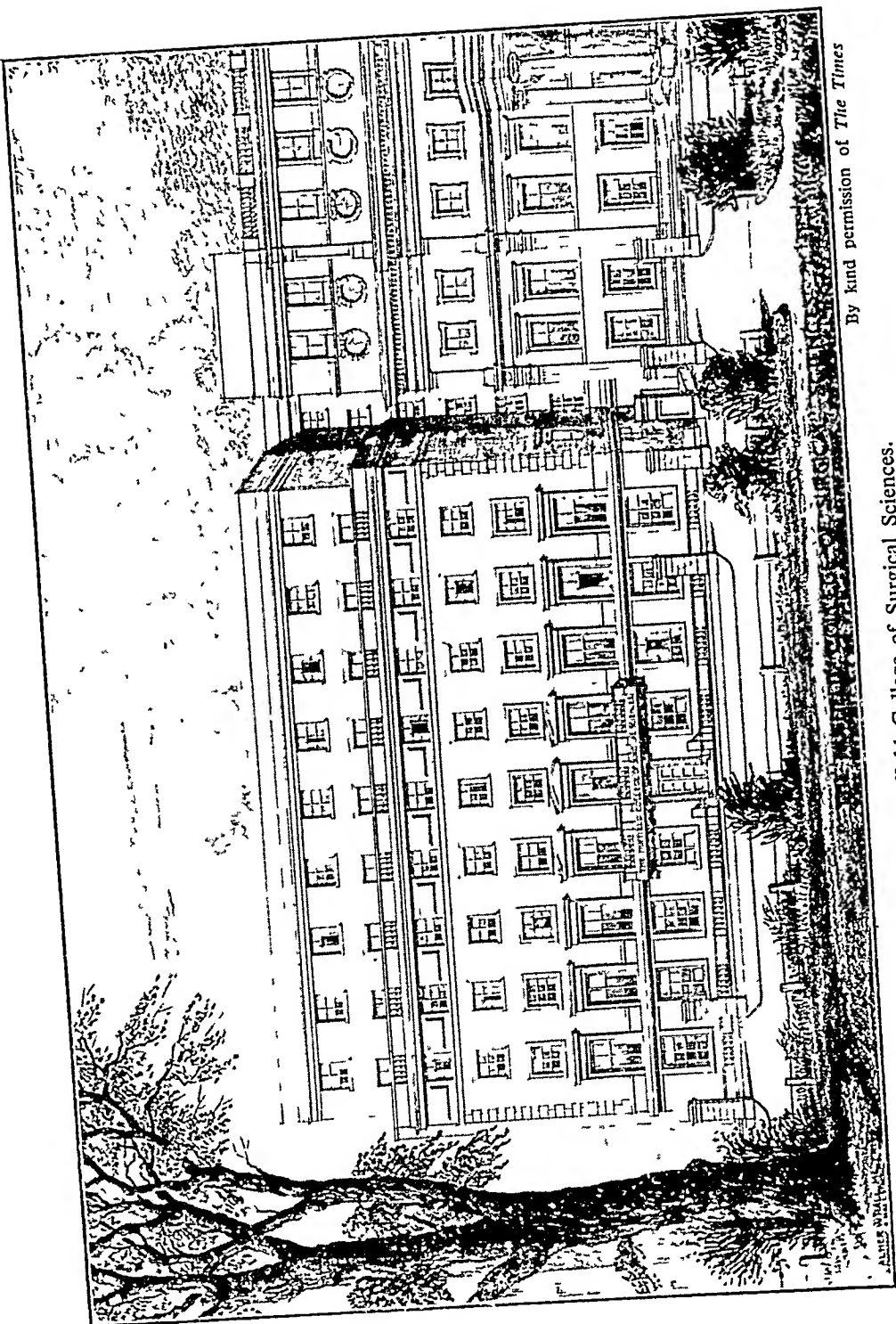
In his response Lord Nuffield said that the two branches of medicine which had always interested him were orthopædics and anæsthetics. When he first proposed to establish chairs in these subjects, it was suggested that such chairs were unnecessary: but, now these specialties occupied a worthy position. Though he had not been able to become a surgeon, he thought he had been born to be interested in medicine and surgery. He did not know any profession in which there had been more jealousy; but those days had passed. He was very pleased to see a number of men from the Dominions present: this country welcomed them with open heart.

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The plans for the Nuffield College of Surgical Sciences are reaching an advanced stage, but it will be some little time before a contract for building can be placed. It is, therefore, a great satisfaction to the Council that the temporary Residential College has been completed, for there was a great demand for the facilities and amenities which residence in the College provides, and those who have been privileged to go into residence have been very appreciative of the advantages which they have gained thereby.

The amenities of the Nuffield College of Surgical Sciences will be on a much larger scale. The plans include the provision of a Squash Court and Billiard Room, Common Rooms, Writing and Reading Rooms. In addition to the necessary dining rooms and administrative offices and advisory bureau, there will be direct communication with the main administrative part of the College, from which access will be obtained to the museums and library, and the laboratories of Anatomy, Physiology, and Pathology. There will be between 70 and 80 bed-sitting rooms. Accommodation will also be provided for residential quarters for the President and for the Warden.

A picture of the proposed Nuffield College of Surgical Sciences appears on the opposite page.



By kind permission of *The Times*

The Nuffield College of Surgical Sciences.

# “OBSERVABLES” AT THE ROYAL COLLEGE OF SURGEONS

## 19. THE BLANE MEDAL

IN 1830, SIR GILBERT BLANE—a distinguished Physician, a Baronet and a Fellow of the Royal Society—transferred to the College £300 invested in “the sweet and elegant simplicity of the three per cents.” The income from the gift was to provide gold medals for Medical Officers of the Royal Navy for specially meritorious professional services, and its existence is a constant reminder to those Officers that they are primarily doctors. The adjudication of the award rests with the Presidents of the Royal College of Physicians, and the Royal College of Surgeons, and the Medical Director-General of the Royal Navy.

In the collection of medals and medallions in the Main Hall of the College there is the Blane Medal which was awarded in 1880 to Henry Frederick Norbury, who later became Medical Director-General of the Navy and a K.C.B. It was presented by his son, Mr. L. E. C. Norbury, senior Vice-President of the College.



Gilbert Blane was born at Blanefield in Ayrshire. He was educated at Edinburgh University and, soon after moving to London, became private physician to Admiral Lord Rodney, to whom he was recommended by William Hunter. In 1779 Blane accompanied Rodney to the West Indies and on other expeditions and served with great distinction. He was a fine sailor and, in the battle against the Spaniards for the relief of Gibraltar, was wounded when conveying Rodney's orders to the gunners. Of his medical services Rodney wrote as follows: “To Blane's knowledge and attention it was owing that the English Fleet was, notwithstanding excessive fatigue and constant service, in a condition always to attack and defeat the enemy.”

When at sea Blane improved the health of the Fleet by attention to the diet of the sailors and by enforcing proper sanitary precautions. It was largely due to his efforts when he became Chairman of the Navy Medical Board that in 1795 the Lords Commissioners of the Admiralty were induced to make the use of lime juice compulsory as a preventive measure against scurvy. The discovery of the value of lemon juice for the prevention and treatment of scurvy had been described by James Lind in 1754 in his "Treatise on the Scurvy," but, before reproaching the Lords of the Admiralty for taking 40 years to order the general adoption of Lind's recommendations, it should be borne in mind that physiologists did not discover the existence of Vitamin C until 150 years after Lind's observation.

After returning from his expeditions with Rodney, Blane was appointed Physician to St. Thomas's Hospital in 1783. He was appointed Physician Extraordinary to the Prince of Wales in 1795, and in 1812 he was made a Baronet for the services he rendered in connection with the return of the Walcheren Expedition.

A novel by Shirley Murrell with the title of "Physician Extraordinary," which has recently been published by Hodder and Stoughton, gives a full account of Blane's life and adventures. W-J.

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## SAYINGS OF THE GREAT

"The proper function of a university is the imaginative acquisition of knowledge . . . A university is imaginative or it is nothing—at least nothing useful."—*A. N. Whitehead, O.M.* (Submitted by Douglas Robb, F.R.C.S., of Auckland, New Zealand.)

"We like to suppose ourselves easily receptive of a the new, and that we are so by virtue of a natural mechanism. Unfortunately this is the exact opposite of the truth. The mind likes a strange idea as little as the body likes a strange protein. and resists it with a similar energy. It would not perhaps be too fanciful to say that a new idea is the most quickly acting antigen known to science."—*Wilfred Trotter.* (Submitted by Douglas Robb, F.R.C.S., of Auckland, New Zealand.)

"Darwin has forced upon us the alternative of being descended from angels or monkeys."—*Disraeli.*

"He who hateth correction is a fool."—*Proverbs.*

*Note.*—Contributions are invited.

## MONTHLY DINNERS

Monthly dinners are held in the College on the Wednesday before the second Thursday of each month. The following are entitled to attend with their guests: All Diplomates and students of the College, and Members of the Associations linked to the College through the Joint Secretariat. It is not necessarily intended that guests should be members of the medical profession.

The dinners will be at 7 p.m. on the following Wednesdays : October 12, November 9, and December 7, 1949, January 11, February 8, March 8, April 12, May 10 and June 7, 1950. There is an inclusive charge of £1 5s. (including drinks), which must be sent with the application to the Assistant Secretary at least a week before the date of the dinner. The dress is Lounge Suit or Uniform.

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### DIARY FOR JULY (15th-22nd)

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|----------|--|
| Fri. 15  | Board of Faculty of Dental Surgery.<br>D.O.M.S. Examination (Part II) and D.I.H. Examination (Part I) begin. |
| 11.00    | Faculty of Dental Surgery Elections.   |
| 3.00     | Faculty of Dental Surgery Elections.   |
| 3.00     | Annual General Meeting of Faculty of Dental Surgery.   |
| 3.45     | PROF. KURT THOMA—Charles Tomes Lecture, Part I : Odontogenic Tumours of the Jaws.*                           |
| 5.00     | PROF. KURT THOMA—Charles Tomes Lecture, Part II : Osteogenic Tumours of the Jaws.*                           |
| 8.00     | Second Anniversary Dinner of the Faculty of Dental Surgery.  |
| Mon. 18  | 5.00 COLONEL J. L. BERNIER, U.S.A.A.F.—Oral Carcinoma.*  |
| Thur. 21 | D.T.M. & H. Examination begins.  |
|          | 7.30 Dinner to the International Committee of the International Congress of Otolaryngology.                  |
| Fri. 22  | D.I.H. Examination (Part II) begins.   |
|          | 9.00 Reception to Fourth International Congress of Otolaryngology.   |

\* Not part of courses.

There will be no lectures at the College during August but the Museums and Library will remain open.

# ODONTOGENIC AND OSTEOGENIC TUMOURS OF THE JAWS

Charles Tomes Lecture delivered at the Royal College of Surgeons of England  
on

15th July, 1949

by

Kurt H. Thoma, D.M.D., F.D.S.R.C.S.

Professor of Oral Surgery, Emeritus; Charles A. Brackett, Professor of Oral Pathology,  
Harvard University

I AM GREATLY honoured to be invited to give the Tomes Lecture before the Faculty of Dental Surgery of the Royal College of Surgeons. There is no need for me to state that in the United States we hold this College in the highest esteem, and it is my personal opinion that the establishment of the Faculty of Dental Surgery in this College has set a new milestone which marks an era of closer co-operation and understanding between general and dental surgery. Thus a solid foundation has been laid for great progress in the basic sciences and applied medical techniques that relate to our field.

Besides being honoured by your invitation, it gives me great pleasure to deliver my address from this beautiful lecture table, which, I understand, was presented last year by a very special friend of mine, Dr. Arthur Allen, then president of the American College of Surgeons.

In classifying tumours of the jaws according to pathogenesis, we recognise two important divisions: those derived from the tooth-forming tissues—odontogenic tumours, and those which are produced by osteogenic cells—osteogenic tumours. It should be mentioned, however, that there is also a miscellaneous group of tumours which are non-odontogenic and non-osteogenic in nature, being formed from other tissues such as nerves, blood vessels and marrow cells, from displaced cell rests, or cells which may have been transported from a primary neoplasm to the jaw by way of the lymphatics or blood circulation.

After the derivation of a particular tumour cell is recognised, other characteristics may be noted. Firstly, the state of differentiation of the cell. Its evolution may be arrested at any stage of its natural transformation and it also may differentiate according to the hereditary factors of its mother tissue. Since the primitive ectodermal epithelial cells of the oral cavity have both odontogenous and adenogenous characters, the determiners which would ordinarily produce ameloblasts may, as we will see, in tumour formation produce glandular tissue, or even melanin.

Secondly, note carefully the arrangement of the tumour cells. They may grow without showing any specific pattern in cords or sheaths, or they may have a tendency to organise in a manner seen in their natural development.

Thirdly, observe the deposit of intercellular substances, such as mucin, collagen, osteoid, enamel, dentine, cementum and bone, and whether the



cellular relationship to these substances is that seen in the normal organ, or whether the arrangement is abnormal and bizarre.

Fourthly, the effect of the parenchymal part of the tumour on the stroma should be observed, Epithelial cells in most cases incite a proliferating activity in the connective tissue. In many instances, however, this reaction takes on major significance and tumour formation occurs. In an adamantoblastoma, the connective tissue cells may differentiate in a similar manner as seen in the tooth development, and thus a mixed odontogenic tumour results, which develops into a soft or hard odontoma.

Fifthly, the effect of the tumour on the host is of greatest importance. Some tumours are encapsulated, expanding the bone as they grow. Others are locally infiltrative, destroy bone and invade the surrounding tissue. Still others grow in lymph or blood vessels and thus metastasise to the lymph nodes or major organs of the body.

### ODONTOGENIC TUMOURS OF THE JAWS

The possibility of variants in tumours formed from tissue derived from the tooth germ gives the pathologist a great opportunity for conjecture and investigation. Not only are the tissues of the tooth derived from two different germ layers, but the development of the involved cells may undergo complete or incomplete transformation. Thus we may have various forms of simple tumours, derived from either the epithelial or mesenchymal tissue, or mixed tumours of great complexity which may contain all types of cells occurring in odontogenesis as well as their calcified by-products. The following table presents a classification according to their pathogenesis :

#### *Ectodermal Origin*

1. Follicular cyst
2. Adamantoblastoma
  - a. Masses of cells
  - b. Cords and buds
  - c. Follicles
  - d. Follicles with cysts
3. Adenoadamantoblastoma
4. Melanoadamantoblastoma
5. Malignant adamantoblastoma

#### *Mesenchymal Origin*

1. Odontogenic myxoma
2. Odontogenic fibroma
  - a. Cementoblastoma
  - b. Dentinoma
3. Odontogenic fibrosarcoma

#### *Mixed Odontogenic Tumours*

1. Adamantinofibroma
2. Adamantino-odontoma
3. Odontoma
  - a. Geminated
  - b. Compound
  - c. Complex
4. Adamantinosarcoma

## ODONTOGENIC TUMOURS OF ECTODERMAL ORIGIN

Follicular cysts and the adamantoblastomata are the most common examples of ectodermal odontogenic tumours. Though the idea is not accepted by all oral pathologists, I feel that follicular cysts should be included here, since they are in many ways closely related to the adamantoblastomata. Not only may cysts develop from epithelial buds derived from the dental lamina or given off from an enamel organ (primordeal cyst), but they may also form by transformation of an enamel organ (dentigerous cyst), just as cysts may form in the follicles of an adamantoblastoma. On the other hand, adamantoblastomata may form from cystic epithelium by growing from the basal layer into the connective tissue membrane beneath. Another characteristic of follicular cysts which allies them to tumours is their tendency to become multiple (multilocular cysts) and to recur after excision.

*Follicular Cysts.*—In these cysts, the epithelium is of the pavement type, which shows the tendency to grow on the surface. The accumulation of fluid and through it the expansion of the lesion may follow, a mechanism which has recently been studied and discussed by Toller (1948).

The treatment of cysts should consist of complete enucleation of the cyst membrane. Cysts so treated generally do not recur, and there is good reason for removing the entire membrane. The arguments for its partial retention have been nullified by a new procedure of obliterating the space by means of gelfoam, which minimizes the danger of infection and saves weeks of post-operative care.

*Adamantoblastoma.*—The tumour may develop from the basal layer of the ectodermal epithelium covering the alveolar process (Fig. 1A), from the enamel organ of a developing tooth, from epithelial remnants in the periodontal membrane (Fig. 1B), or from the membrane of a follicular cyst (Fig. 1C). Variations in arrangement of the epithelial cells has been well described by Ch'in (1938)?.

The epithelium may grow in the form of cords which tend to give off buds (Fig. 2A), sometimes forming a plexiform pattern (Fig. 2B). In some cases (Fig. 2C), undifferentiated masses of cells may form. In most cases follicles develop. The latter are arranged according to the fashion seen in the enamel organ, except that they are irregular in shape and do not as a rule produce a reaction in the adjacent mesenchyma (Fig. 2D). In the most highly differentiated type, cylindrical cells form a lining at the periphery, while the central ones show stellate arrangement. In some, squamous cells are found (Fig. 2E), while in others cystic degeneration occurs (Fig. 2F). Other histologic variations may be recognized. In the adenoadamantoblastoma, which is of rare occurrence, the cells tend to differentiate along glandular patterns (Fig. 3A), while in the melanoadamantoblastoma, melanin is formed by some of the epithelial cells (Fig. 3B). Little is known about the malignancy of the melanoadamantoblastoma. Only a very few cases have been reported. One has been seen by Mummery and Pitts (1926)<sup>3</sup>, and two have been studied at the

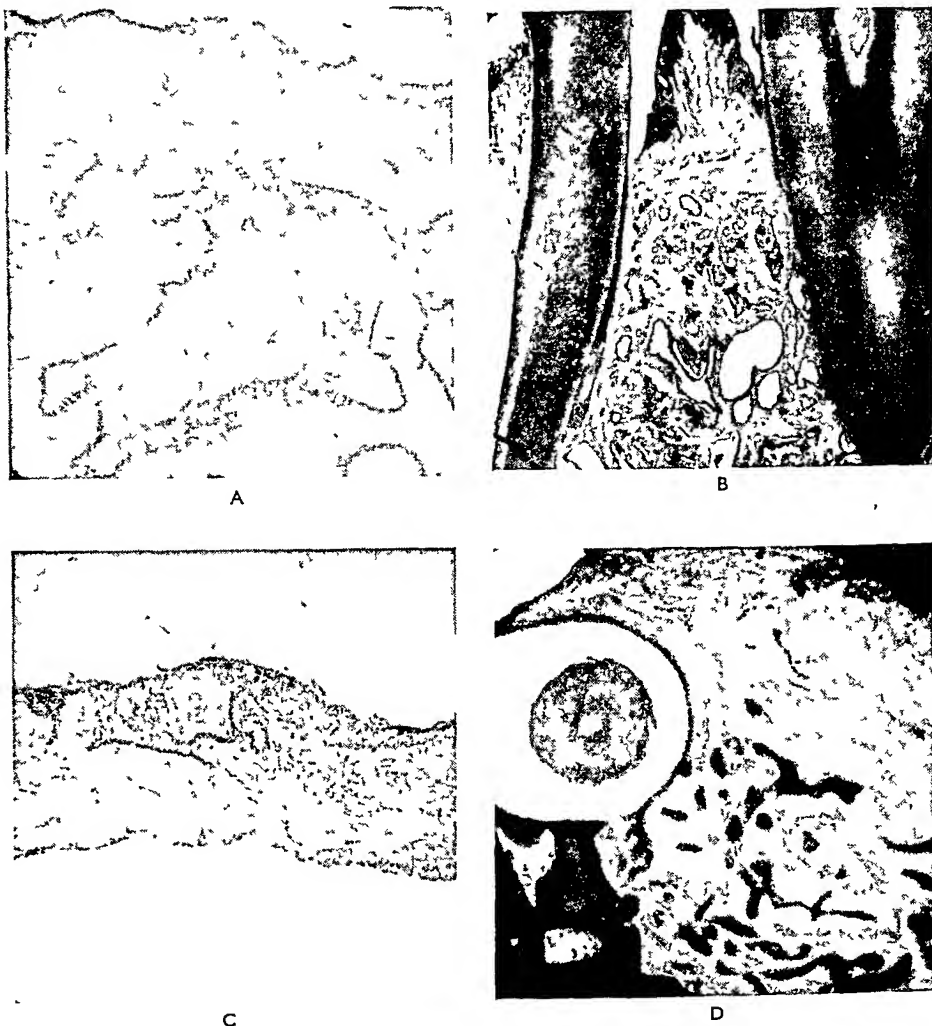


Fig. 1. Epithelial Odontogenic Tumours: Place of origin of adamantoblastoma. A.—from basal layer of surface epithelium; B.—from cell rests in peridental membrane; C.—from epithelial lining of cyst; D.—from epithelial structures in odontoma.

Institute of Pathology of The United States Army.\* The pigment forms in the epithelial component of the tumour and may extend into the stroma and cause a bluish-black discolouration of the mass.

The roentgen diagnosis of adamantoblastoma is not always easy. In some instances a "honeycomb" effect is seen. This is due to the infiltration of the spongiosa by tumour tissue without destroying all the bone trabeculae. The polycystic type is generally easily recognised. The monocystic type is difficult to differentiate from a follicular cyst. In the former, we may see indentations at the margin of the defect, the presence of peripheral daughter cysts, the inclusion of tooth roots in the area, or

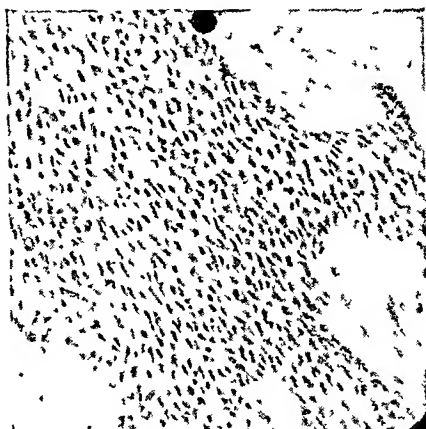
\* Courtesy Lt-Col J. L. Bernier.



A



B



C



D



E



F

Fig 2. Epithelial Odontogenic Tumours: Differentiation and arrangement of cells in various types of adamantoblastomas. A.—cords; B.—plexiform arrangement; C.—sheaths; D.—follicles; E.—follicles with squamous cells; F.—cystic formation in follicles.

the formation of calcified tissue ; in the latter, we find displacement of adjacent teeth and generally a complete cystic margin. It should be noted that many follicular cysts appear to be multiple, due to large partial septæ which subdivide the cavity.

*Malignant Adamantoblastoma.*—While adamantoblastomata are locally invasive and show great tendency to recur after operation, they do not in general cause metastases. However, a few cases have been reported in which metastases occurred. (Eve-Parker, Ewing, Horsey, Simmons, and Spring.) In reviewing lung metastasis Waterworth and Pullar (1948)<sup>4</sup> found that out of seven reported cases only one was histologically confirmed. They reported a case of their own which recurred twice, and when pulmonary symptoms occurred, a thoracotomy was done which disclosed a tumour similar to that in the jaw but with more mitoses.

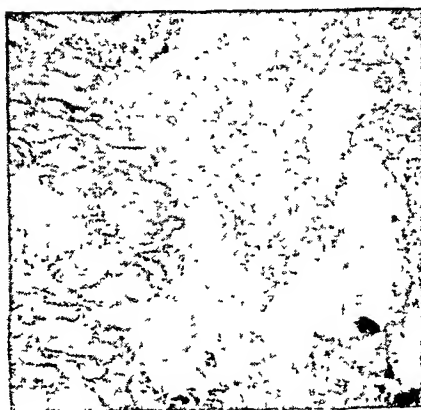
Of course, pulmonary metastasis in cases operated on may be due to aspiration of tumour cells. A case of lung metastasis from The Institute



A



B



C

Fig. 3. Epithelial Odontogenic Tumours : A.—adeno-adamantoblastoma ; B.—melano-adamantinoma ; C.—lung metastasis.

of Pathology of The United States Army is shown in Fig. 3C. Carcinomatous changes have been reported by Kaufman (1922)<sup>5</sup>, and others. In the recent literature, Lindemann (1948)<sup>6</sup> reported a maxillary adamantoblastoma which recurred 12 years after operation; it involved the orbit and base of the skull and was combined with solid carcinomatous tissue. He pointed out that in adamantoblastoma the usual five years of observation is not sufficient to safeguard the patient; examination should be carried out for a much longer period of time.

### ODONTOGENIC TUMOURS OF MESENCHYMAL ORIGIN

While epithelial odontogenic tumours have been recognised for a long time, little has been written about the possibility of pure tumours arising from the mesenchymal part of the tooth germ, the dentine papilla, and the dental follicle.

*Odontogenic Myxoma.*—The myxoma which occurs as a central tumour in the jaws has certain characteristics that distinguishes it from myxoma seen in long bones, which tends to recur and become malignant. Thoma and Goldman (1947)<sup>7</sup> have recently pointed out that most myxomas of the jaws are benign and therefore may have a different origin from those in the rest of the skeleton, being formed from the mesenchymal part of the tooth germ rather than from cells which are destined to embark on an osteogenic career. The theory may be based on the fact that the cellular elements of a myxoma (Fig. 5A) resemble the spindle-shaped and stellate cells of the tooth germ, which are of a primitive type producing no collagen or elastic fibres even though in the myxoma certain cells may reach greater differentiation and produce collagen fibres which classifies them as fibro-myxoma. If, on the other hand, you subscribe to the opinion that a myxoma is a modified form of a fibroma, the theory still holds because the tumour then may be considered a fibroma derived from embryonic or adult mesenchymal cells of the tooth germ, such as the periodontal membrane, and has undergone a myxomatoid change or degeneration.

To further substantiate this view, we pointed out that these tumours, like adamantoblastomata, are frequently associated with unerupted or congenitally missing teeth. In most of our cases such a relationship could be established. In cases reported by others, specific mention of similar conditions has been made. Fuste and Mena-Sera (1941)<sup>8</sup> reported a case with an unerupted tooth. Milhorn and Parkhill (1946)<sup>9</sup> reported a tumour appearing in the X-ray as a dentigerous third molar cyst. Stafne and Parkhill (1947)<sup>10</sup> described a case in which the tumour was in an area below an unerupted third molar in the mandible. One case of mine (Fig. 4) developed from a "cystic area" below a first molar, which had been incompletely removed. I believe that the odontogenic myxoma is seemingly a benign tumour which, however, may involve a large part of the jaw. In the X-ray it has either a "honeycomb" type of appearance (Fig. 4), or resembles a cyst. Some have a decidedly invasive



Fig. 4. Mesenchymal Odontogenic Tumour: Roentgenogram of odontogenic myxoma.

character, even though malignancy cannot be demonstrated. Excision should be radical, although resection of the jaw is not indicated.

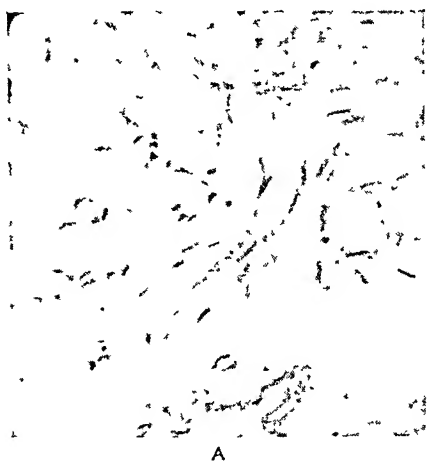
*Odontogenic Fibroma.*—This tumour, like the myxoma, may arise from the mesenchymal part of the tooth germ, including the periodontal membrane. It is, therefore, frequently associated with the roots of a tooth. The cells attain a higher differentiation than in the myxoma. The tumour is made up of connective tissue cells producing collagen fibres, and cementicles and bone trabeculae may form (Fig. 5B). It may expand and involve a large part of the mandible.

*Cementoma.*—In some odontogenic fibromas, some cells develop into cementoblasts—cementoblastomata—and lay down cementum in the form of cementicles (Fig. 5C) or osteocementum in the form of trabeculae. The entire mass may be transformed into calcified cementum, reducing the cellular part to an encapsulating membrane (Fig. 5D).

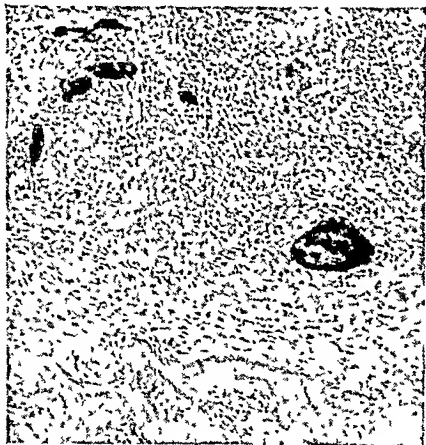
*Dentinoma.*—In a similar manner, odontoblasts may form from the odontogenetic mesenchymal cells and thus a dentinoma may result (Fig. 5E).

*Odontogenic Fibrosarcoma.*—A malignant type of connective tissue tumour may arise from the odontogenic mesenchyma. I have a patient who has gone nine years without recurrence after a block excision of a fibrosarcoma attached to the dental follicle of an unerupted third molar

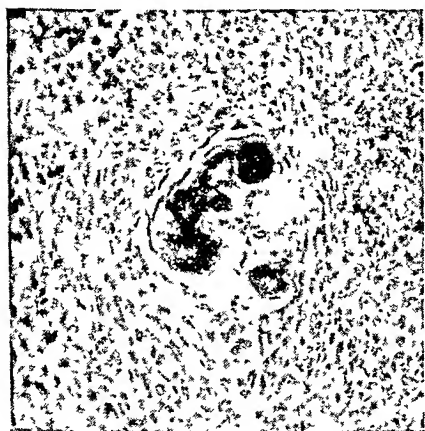
# ODONTOGENIC AND OSTEOGENIC TUMOURS OF THE JAWS



A



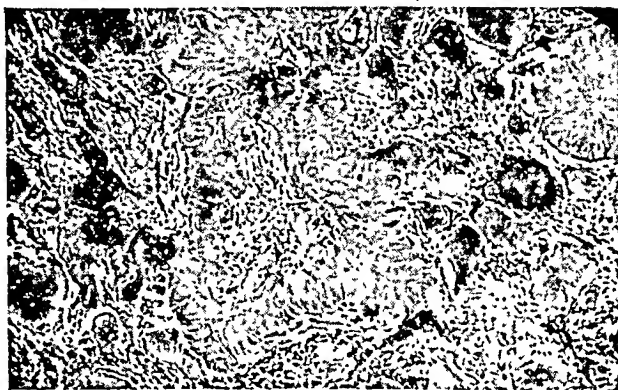
B



C



D



E

Fig. 5. Mesenchymal Odontogenic Tumours: Differentiation of cells and formation of intercellular substance. A.—odontogenic myxoma; B.—odontogenic fibroma; C.—cementoblastoma; D.—cementoma; E.—dentinoma.



tooth. The tumour was completely cellular with many cells undergoing mitosis.

### MIXED ODONTOGENIC TUMOURS

Calcified mixed odontogenic tumours, so called odontomata, have been discussed extensively in the literature; however, only more recently has it been recognised that these are end products and form from tumours made up of epithelial and mesenchymal components that arise from the tooth germ. These remain either in an immature state of cell development (soft odontoma), or produce more highly differentiated tissues such as enamel, dentine, and cementum. These more highly differentiated tissues, of course, are formed from cells such as are seen in normal tooth development, ameloblasts, odontoblasts, and cementoblasts. They have the same inductive effects upon one another as is seen in the formation of a normal tooth. Odontoblasts are formed only against a layer of ameloblasts as Glasstone (1935)<sup>11</sup> has pointed out, but enamel is formed only if the ameloblasts are polarized by the deposit of dentine. The proof of this is found in the observation of Sprawson (1937)<sup>12</sup> who believes that no enamel is formed in an adamantoblastoma because no dentine is present. However, in our study of odontogenic tumours (Thoma and Goldman, 1946)<sup>13</sup>, we found that dentine, like cementum, can be produced despite the absence of the odontogenic epithelium, while enamel did not occur in any of the purely epithelial tumours. So-called enamelomas do not form independently. They are always attached to the root of a tooth which indicates a mesenchymal influence in their formation. So-called enamel drops, which are unattached, are odontomata containing dentine and pulp.

*Adamantinofibroma.*—This is a so-called soft odontogenic mixed tumour made up of epithelium and connective tissue. The latter instead of being scanty as in adamantoblastoma takes on a predominant role. It is cellular in some cases with a tendency to form stellate cells resembling the dental pulp in others producing collagen fibres (Fig. 6), while the epithelium is seen in the form of budding strands rather than the extensive follicular arrangement with columnar basal cells. The tumour is frequently associated with an unerupted tooth, and under X-ray examination appears as an osteolytic defect, which is often cystic in nature.

*Adamantino-odontoma.*—In some instances, calcified structures form in the adamantinofibroma. The tumour may give the appearance in the X-ray of an odontoma, though on microscopic study epithelial elements are seen. These have the power to proliferate, invoke connective tissue response and cause expansion of the tumour mass. This is of great importance from a clinical point of view, because such tumours have a tendency to invade and recur if not completely removed by surgery. I have many cases of this type. One in the mandible, another in the maxilla (Fig. 7) will be presented.

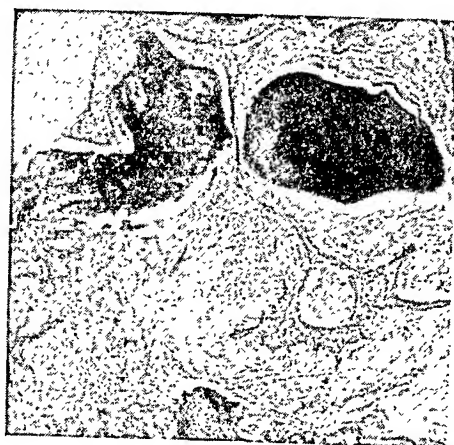
*Odontoma.*—This term should be applied to the completely calcified tumour in which the odontogenic cellular tissue has become atrophied



Fig. 6. Mixed Odontogenic Tumour : Adamantinofibroma.



A



B

Fig. 7. Mixed Odontogenic Tumour : Adamantino-odontoma of maxilla.  
A.—Roentgenogram ; B.—photomicrograph showing bone, cementoma and adamantoblastoma.

and will not continue to develop. While this state may seldom be achieved completely, at least there are cases in which little soft tissue remains and where on X-ray examination, the osteolytic defect in the bone is filled entirely with calcified structure, enamel, dentine and cementum. Enamel organ tissue, pulp, and periodontal membrane have ceased to produce intercellular structures. Odontomata have been classified into geminated, compound composite, and complex composite varieties, a classification which has stood the test of time and need not be elaborated upon further.

*Adamantinosa coma.*—Mixed odontogenic tumours may develop malignancy; this, however, is rare. The malignant component is the mesenchymal part, so that a fibrosarcoma develops in which adamantinomatous tissue of the usual type may be seen. The first case was published by Heath<sup>14</sup> in the *British Medical Journal* in 1887. Krompecher (1917)<sup>15</sup>, reported another one, and still another was described by Wigdorschunk (1932)<sup>16</sup>.

### TREATMENT

The treatment of odontogenic tumours depends on the type, size, and the amount of jaw involved, and especially on the characteristics of the neoplasm. In cases of cysts and mature odontomata, and uncalcified mesenchymal tumours which are not malignant, enucleation from an intra-oral, and in rare cases, an extra-oral approach generally gives good results. The operative defect in the bone may be filled with gelfoam saturated with a penicillin thrombin solution (Fig. 8). It allows the wound to be closed by sutures and eliminates post-operative dressings.



Fig 8 Fibrin Foam inserted into cavity after cystectomy. A—cyst of mandible; B—insertion of Fibrin Foam.

In the adamantoblastoma, because of the invasive character of the odontogenic epithelium and the tendency to recur, the surgical interference should be radical. With adamantoblastomata that are multilocular, and particularly when the patient gives a history of one or more previous operations, as well as in malignant mesenchymal tumours such

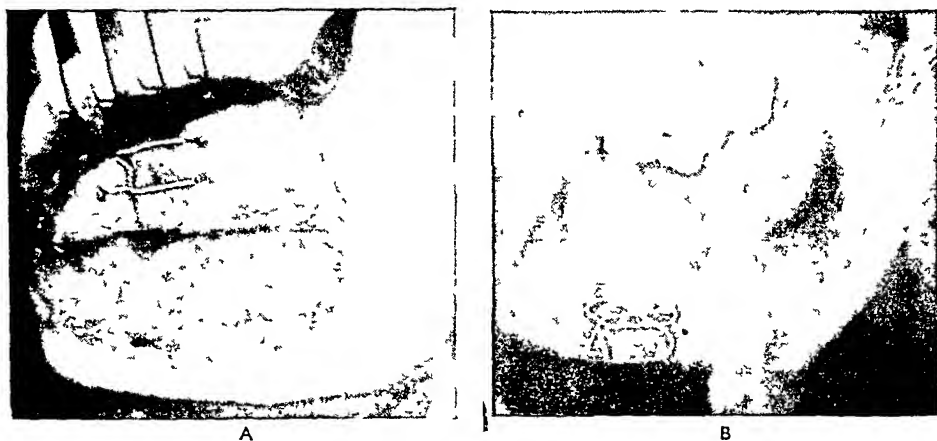
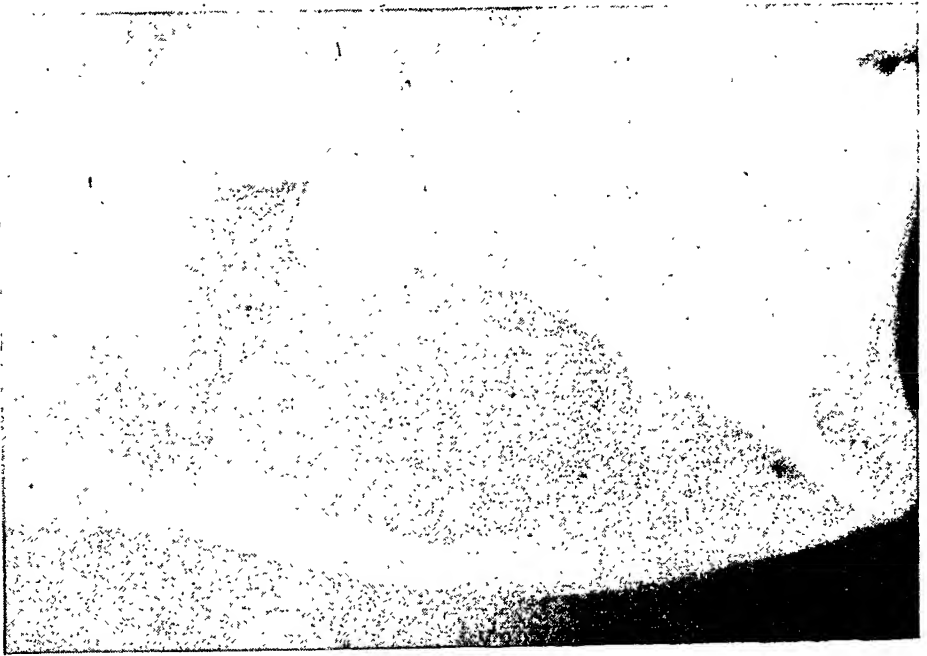


Fig. 9. Bone graft from ilium to replace part of mandible excised for adamantoblastoma. A.—insertion of bone graft; B.—post-operative Roentgenogram.

as the fibrosarcoma, the segment containing the tumour should be resected and replaced by means of a bone graft (Fig. 9). Early cases lend themselves to block resection without disturbing the continuity of the jaw.

In some benign mesenchymal tumours, such as the central fibroma and myxoma, complete decortication may give sufficient access to the field of operation, to permit the removal of all neoplastic tissue, thus leaving the lingual plate of the jaw for regeneration. In some adamantoblastomata it is possible to remove the mass by means of a peripheral osteotomy (Fig. 10A). In this operation, the inferior border of the horizontal ramus and the posterior border of the ascending ramus, which frequently are uninvolved and can be thoroughly debrided, are retained. The coronoid process as a rule must be sacrificed, which requires dividing the tendon of the temporal muscle, but the condyle may remain. This assures a well-functioning jaw. After this procedure, considerable bone regeneration takes place (Fig. 10B), but if desired, the vertical dimension of the jaw can be improved immediately by the use of an implant of tantalum gauze placed on the top of the ridge (Fig. 11). With either method, a useful alveolar ridge may be obtained.

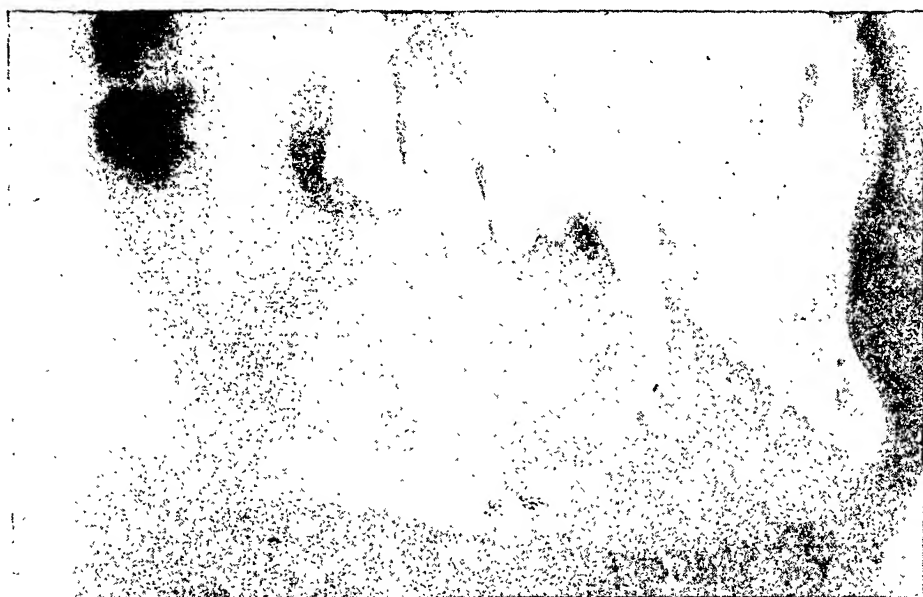


A

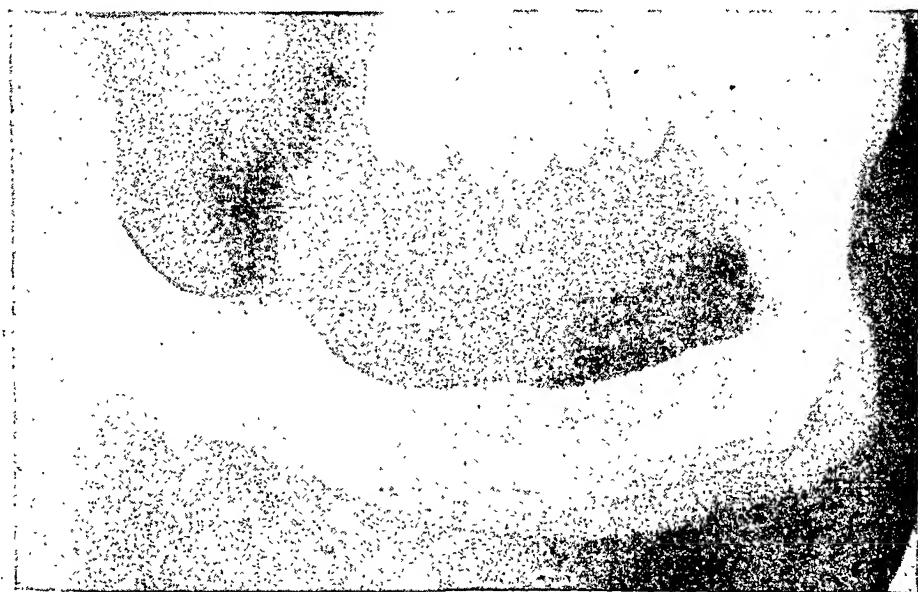


B

Fig. 10. Peripheral osteotomy. Roentgenogram of adamantoblastoma of mandible; A.—post-operative Roentgenogram of mandible; B.—Roentgenogram taken two years later showing bone growth.



A



B

Fig. 11. Peripheral osteotomy. A.—Roentgenogram of adamantinofibroma ; B.—post-operative Roentgenogram showing Tantalum gauze insert.

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*Note.*—The second part of Professor Thoma's Charles Tomes Lecture will be published in Vol. 5, No. 3.

# THE GENERAL PATHOLOGY OF THE LYMPHADENOPATHIES

Lecture delivered at the Royal College of Surgeons of England

on

6th May, 1949

by

Professor Geoffrey Hadfield, M.D., F.R.C.P.

Sir William Collins Professor of Human and Comparative Pathology  
Royal College of Surgeons of England

IT HAS BEEN a tradition in this College for many years that those who aspire to the distinction of its Fellowship must produce evidence that they possess a sound knowledge of anatomy and physiology. Four years ago the Council made three progressive amendments to their regulations by deciding that the course of study in the basic sciences must take place in the post-graduate period, that far more stress must be laid on the application of physiological principles to disease, and that general pathology must be included as one of the basic sciences. I am sure all of you must have experienced some difficulty in defining for yourselves the scope of general pathology, and it occurred to me that it might be of assistance if I selected a group of diseases of surgical importance with whose individual characteristics you are all familiar and discussed them strictly in terms of general pathology.

I have chosen the lymphadenopathies as a subject chiefly because it does not readily lend itself to simple generalisation and our review will involve excursions into other chapters of pathology to gather relevant evidence. We must, for instance, briefly consider the origin and the general structure and functions of mesenchyme, for lymph nodes are wholly composed of this remarkable tissue. We must also remember when examining one of a group of swollen lymph nodes that we are dealing with a single unit forming an integral part of a highly reactive cellular defence system scattered throughout all the body tissues, and I need not remind you that I am referring to the reticulo-endothelial system, whose main depots are the lymph nodes, spleen and hæmopoietic marrow. These organs are built on the same structural plan (see Figure 1) and their reactions to pathological stimuli are strikingly similar. The system may go into action as a whole or in part. A single lymph node, for example, responds to the same stimuli and exhibits the same range of cellular reaction to irritants carried to it by its own lymphatics as does the whole scattered system when exposed to the same irritant carried in the general blood-stream and to appreciate the changes found in a group of enlarged lymph nodes responding to a local stimulus we must relate them to the origin, structure and function of the whole system of which they are a part.



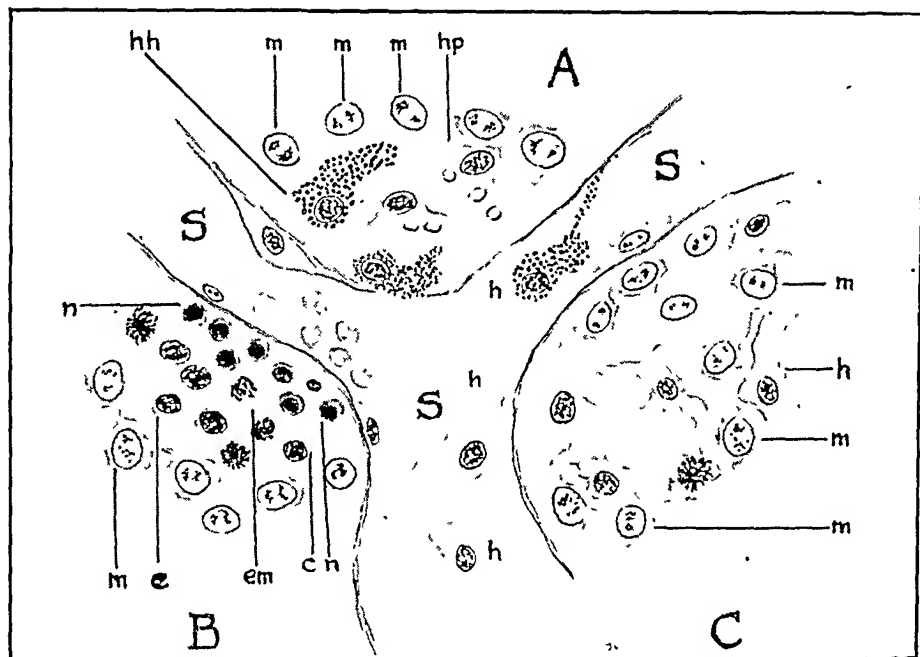


Fig. 1. General Plan of Lympho-reticular Apparatus. (Reticulo-endothelial System.)

*Diagrammatic*

- A. Erythrophagocytosis in spleen pulp.
- B. Erythropoiesis in bone marrow.
- C. Phagocytosis in lymph gland.
- S. Sinus lined by and containing histiocytes (h).
- m. Undifferentiated mesenchymal cells.
- h.p. Histiocyte containing red cells.
- h.h. Histiocyte containing hæmosiderin.
- e. Erythroblasts.
- n. Normoblasts.

The reticulo-endothelial system was identified by repeatedly flooding the blood-stream with intra-vitam dyes, the negatively charged particles of which, being in colloidal solution, are of ultra-microscopic dimensions. After injection the dye particles circulate freely in the plasma from which, after a relatively short time, they are rapidly and completely abstracted and are found as large, easily visible aggregates lying in the *cytoplasm* of the phagocytic cells lining the capillary sinusoids of the spleen, hæmo-poietic marrow and liver, whilst after repeated injections more and more lymph nodes become vitally stained. Frequently repeated injections of foreign particles yield significant information. As the injections proceed, particle-laden phagocytes in increasing numbers crowd into the wide sinusoids of the lymph nodes and many of them migrate into the cellular syncytium in which the sinusoids are embedded. The syncytium is composed of fertile mesenchymal cells lying in the meshes of a network or

reticulum composed of fine fibrils which become deep black after treatment with silver salts (see Figure 2). As long as phagocytosis is active, more and more of the fixed cells lying in the fibrillary reticulum become

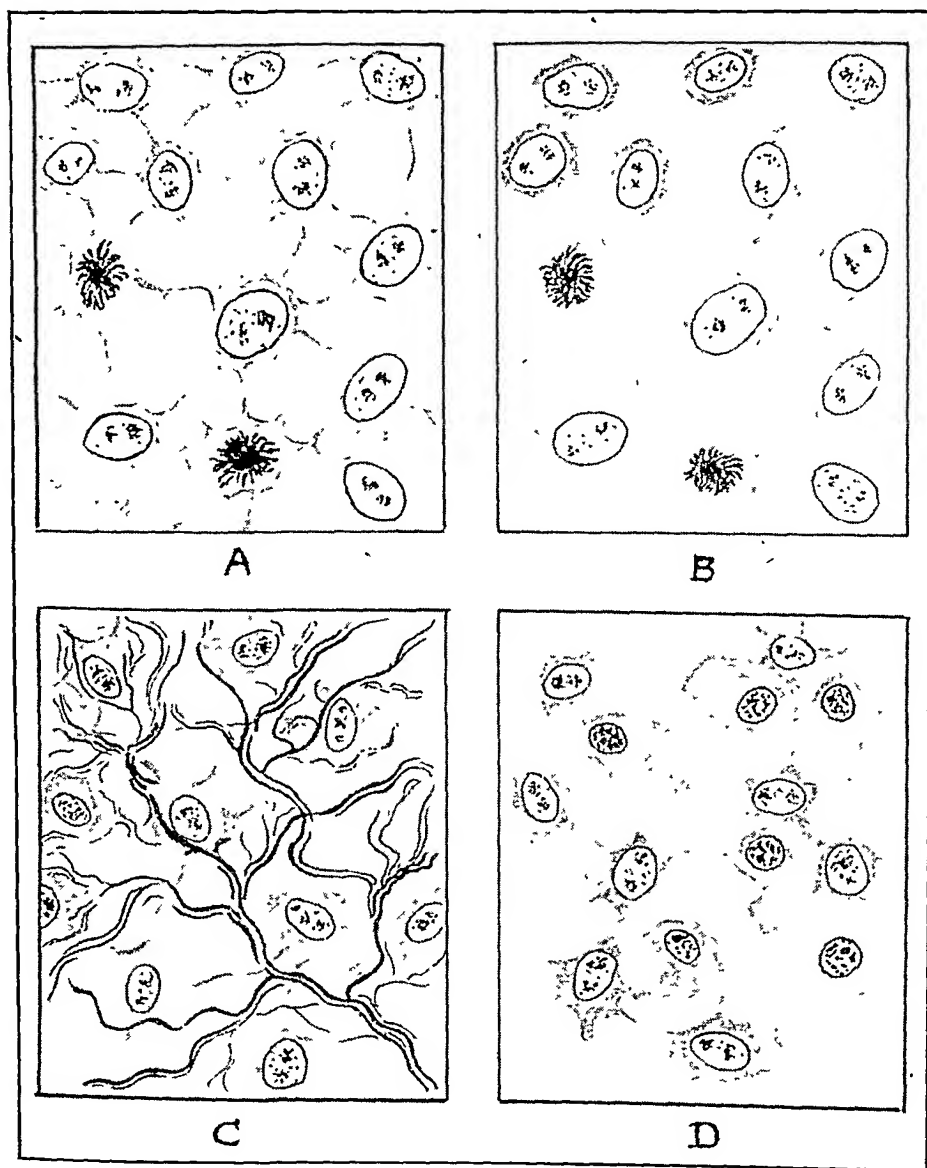


Fig. 2. Primitive Mesenchyme.

- A. and B. As seen in early mammalian embryo.
- A. After intra-vitam fixation.
- B. With delayed or imperfect fixation.
- In A. and B. the intercellular material is fluid.
- C. Development of argyrophil reticulum in whose meshes lie reticulum cells.
- D. Differentiation to produce histiocytic phagocytes.

mobile and migrate into the lumen of the sinusoid, whilst others show clear and pronounced signs of proliferation to supply new phagocytic cells (see Figure 3).

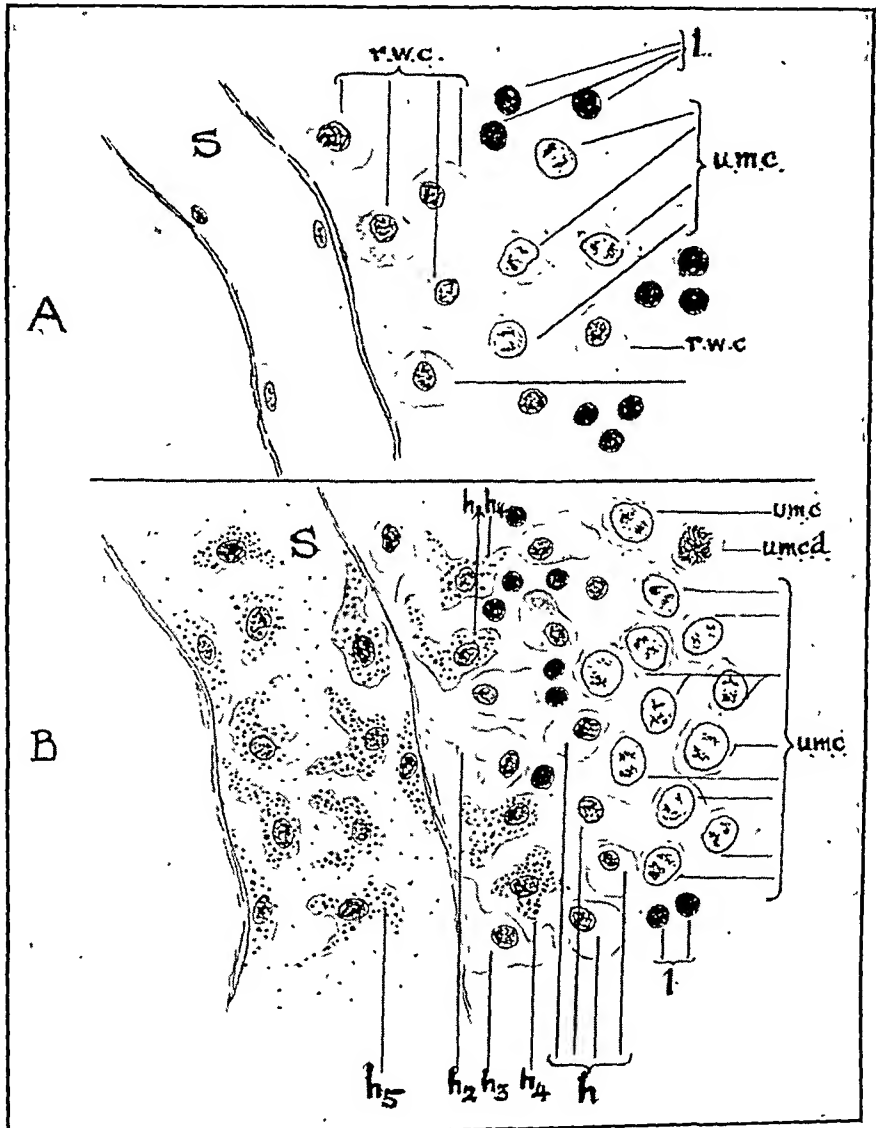


Fig. 3. The Reacting Lymph Node (Diagrammatic).

- A. Cell elements in resting lymph node.
- B. Reacting lymph node.
- S. Lymphatic sinusoid.
- u.m.c. Undifferentiated mesenchymal cells.
- u.m.c.d. Undifferentiated cell in mitosis.
- r.w.c. Resting wandering cells (histiocytes).
- h. Histiocytes, some of which ( $h_2$  and  $h_3$ ) are moving towards sinus; others ( $h_4$ ) filled with particles have left it.
- Sinus in B filled by particle-laden histiocytes ( $h_5$ )

*The striking ability of the primitive and fertile mesenchyme of a lymph node to undergo rapid proliferation is highly characteristic.* In a very large number of diseases in which lymph node enlargement occurs the increased bulk of the node is almost entirely accounted for by the generation of a new cell population which owes its origin to the marked tendency of its undifferentiated mesenchyme to respond to many stimuli by rapid multiplication.

There is every reason for believing that an infinite variety of particles which become dispersed in the blood-stream in disease are dealt with, irrespective of their chemical or biological nature, by the same mechanism as the intra-vitam dyes, always provided that the particles possess the essential property of foreignness to the milieu intérieur, and are of such a size and are dispersed to such a degree that they circulate freely in the plasma. Such particles may obviously have an endogenous origin. The break-down products of the "hæm" fraction of hæmoglobin molecules resulting from the disintegration of senile erythrocytes are dealt with in this way under physiological conditions, and when hæmolysis is excessive the retention in its phagocytic cells of ferrous and ferric oxide maps out the system with the precision of a planned experiment. An identical change is extremely common in the regional lymph nodes draining a localised extravasation of blood. Intermediate products of lipid metabolism, such as cholesterol, cerebroside and phospho-lipid, when present in excessive amounts are similarly abstracted during the course of the lipid storage diseases and are firmly held in enormous quantities in the cells of the system, the lymph nodes being sometimes extensively involved.

Virus particles, bacteria and protozoa and the colloidal break-down products which result from their disintegration in the tissues are dealt with in the same way. It is essential to realise that many of these break-down products, being foreign in origin and protein in composition, are *antigenic*. If the system is presented with living particles in manageable numbers, these are broken down by intracellular digestion within the system into a complex mixture of antigens. In any bacteriæmia or true toxæmia, therefore, the cells of the system come to contain, relative to other tissues, a heavy concentration of antigenic substances. There is no doubt that such cells loaded in this way with antigens manufacture specific antibodies to them within their own cytoplasm. It is not at all improbable, from the work initiated by Sabin, that the antibodies so produced become heavily concentrated at the surface of such cells which, by actually shedding thin surface films of their own cytoplasm, liberate antibody in a free state into the tissue fluid or blood. In the blood antibodies are found exclusively in the  $\gamma$ -globulin fraction of the plasma protein and it is probable that this fraction is composed entirely of antibodies or is exclusively concerned in antibody transport. From experimental evidence the first alternative appears to be the more likely and carries the implication that antibodies as a group are chemically identical with the globulins.

Let us accept the evidence that these antibody-globulins comprising the  $\gamma$ -globulin fraction of the plasma are nothing more than large molecular aggregates which were originally part and parcel of the cytoplasm of living mesenchymal cells. Are we now in a better position to understand how antibodies protect the tissues from the harmful effects of such malignant antigens as the bacterial exotoxins? The most powerful exotoxins are not in themselves poisons in the sense that they exert some crude chemical disruptive action on cell protoplasm. They seem to be harmful by virtue of one single property, namely their *foreignness*. Having regard to its probable origin, nothing could be more *native* than antibody-globulin, and it is impossible to escape the conclusion that an antibody neutralises an antigen by surface adsorption, thereby converting a foreign surface into a native one (see Figure 4). This idea is strongly supported by the fundamental general principle that surface action plays a vital rôle in all biological phenomena. The specificity of the antibody-antigen reaction probably depends on the ability of the globulin molecules to adhere to those of the antigen by developing a suitable physico-chemical surface pattern.

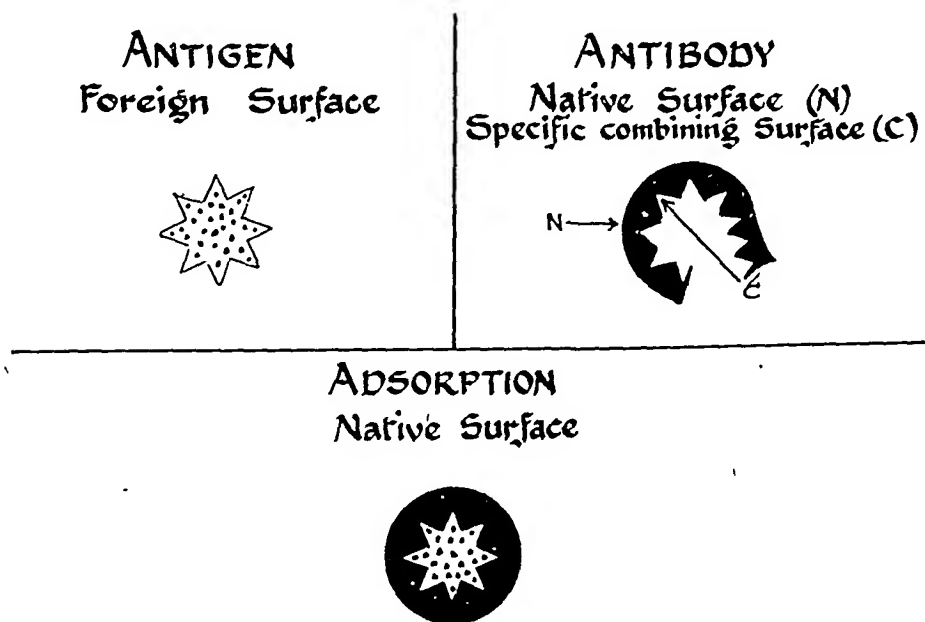


Fig. 4.

If we are right in assuming that the changes in a single reacting lymph node have the same basic significance as the reactions of the whole system to blood-borne antigens, we must assume that the cells of an isolated reacting lymph node are themselves capable of producing antibodies. There is a fair amount of exact experimental evidence which

supports this. The lymph nodes draining an area into which an antigen has been injected have a high content of antibody and investigation of the efferent lymph leaving such nodes shows that its lymphocytes contain much more antibody than the fluid in which they are suspended. Other experiments in immunised animals show that the concentration of antibody is considerably higher in the lymphocytes of their lymph nodes than in their blood plasma and one observer claims that the cytoplasm of lymphocytes contains a globulin identical with the  $\gamma$ -globulin of the animal's blood plasma.

The antibody-globulin produced by the phagocytic cells appears therefore to be transferred to lymphocytes (Figure 5). Its final release to the

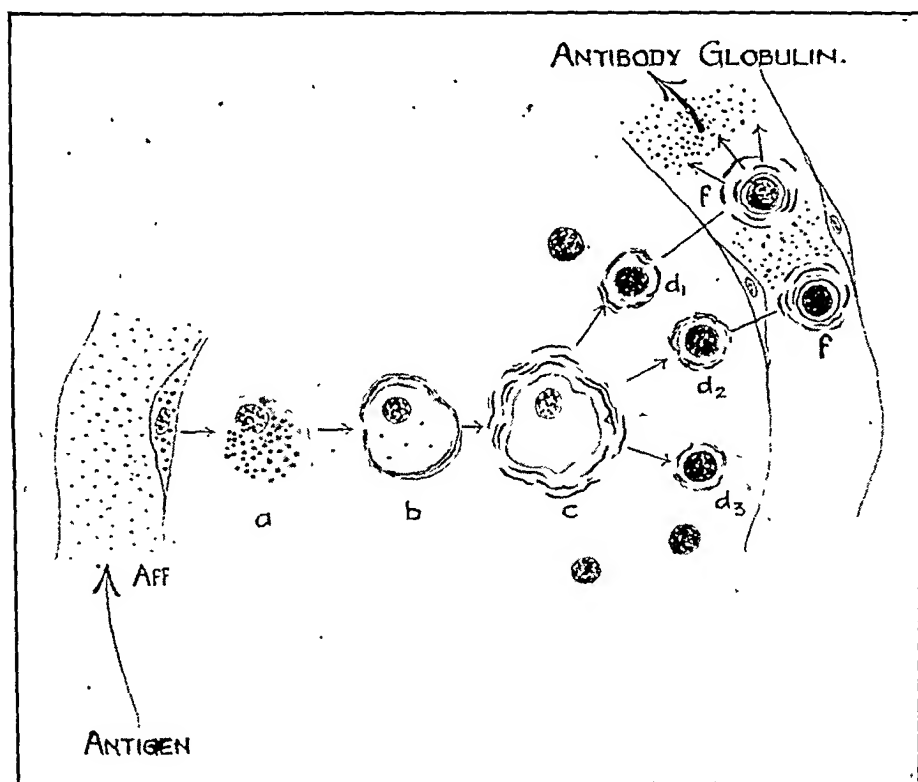


Fig. 5. Possible Sequence in Production of Antibody-Globulin in Lymph Node.

Aff. Particles of antigen entering gland by afferent sinusoid: phagocytosis by sinus lining phagocyte.

a. Migration of phagocyte into reticulum.

b. Large majority of antigen particles lysed: surface concentration of antibody-globulin.

c. Shedding of surface films of globulin.

d<sub>1</sub>, d<sub>2</sub>, d<sub>3</sub> Globulin taken up on surface of lymphocytes.

f. Lymphocytes in blood-stream shedding surface films and liberating globulin to plasma.

blood would seem from another series of experiments to be under the control of the adrenal cortex. Injection of cortical extracts or of the adrenotrophic hormone of the pituitary causes a fall in blood lymphocytes and a rise in the globulin of the plasma. In other experiments a long enough interval was allowed to elapse after injection of an antigen for the antibody content of the blood to fall to a very low level. Cortical extract was then injected and was followed in a few hours by the re-appearance of antibody-globulin in the plasma in appreciable amounts.

These experiments need confirmation and amplification but it is tempting to see in them the answers to three questions which have exercised the minds of pathologists for many years. Firstly, what is the function of the lymphocyte? Secondly, what is the function of the lymph follicle or germinal centre? Thirdly, has the close structural relationship between the cortical lymph follicle of a lymph node and its medullary filtering mechanism some basic functional significance, or alternatively, are the follicles and the medullary filter two totally unrelated tissues which, for purely developmental reasons, happen to be enclosed in a common capsule in the same way as the cortex and medulla of the adrenal?

In the first place the balance of evidence is in favour of regarding the lymph follicle as a focus of lymphopoiesis. The large pale cells which occupy its central part are fertile and undifferentiated. They produce several generations of cells and the final product, the lymphocyte, finds its way into the lymph and blood-streams. The whole structure is therefore comparable in general pattern with the foci of erythropoiesis and leucopoiesis in the marrow and is equally susceptible to irradiation, and to senile atrophy. The fully differentiated lymphocytes forming the periphery of the follicle have in all probability a short life span, possibly of the order of a few days, and there seems little doubt that to maintain their numbers the central undifferentiated mother cells of the follicle must be in a state of almost continuous proliferation.

The total mass of lymphoid tissue in the body is large and widely distributed, being found not only in the lymph nodes but in the sub-epithelial tissue of the whole of the gastro-intestinal and upper respiratory tracts and in all the reticulo-endothelial organs, being especially prominent in the spleen. Wherever lymph follicles are found they have an invariable and intimate relationship with a slowly moving blood or lymph stream conducted along wide sinusoidal capillaries lined by highly reactive phagocytic cells. These considerations led Maximow to propose that Aschoff's *reticulo-endothelial system* is more accurately described as the *lympho-reticular apparatus*. The experiments I have quoted to you, and the results of several others which point in the same direction, suggest that antigen adsorption and intra-cellular lysis with the production of antibody-globulins are carried out by the phagocytic component of the lympho-reticular apparatus. They also suggest that this may involve the whole system when the antigen is blood-borne or only a single group of lymph

nodes when draining an antigen-containing tissue. It would also appear that the antibody-globulin so produced is not at once discharged into the lymph and thence into the general circulation as freely circulating globulin molecules but is taken up and carried in the cytoplasm of the lymphocytes. It may eventually be shown that their final release into the circulation is due to the shedding of surface films of cytoplasm from antibody-laden lymphocytes circulating in the blood. This attractive story is based to some extent on speculation and unconfirmed observations and we must regard it for the time as nothing more than a good working hypothesis. It does suggest, however, that the lymph follicles of the cortex and the filtering mechanism of the pulp of a lymph node are functionally interdependent structures and together form a co-ordinated cellular defence mechanism. It is obvious that if this is true for the lymph nodes it is equally true for all the lympho-reticular tissue in the body. We must also remember that whilst the wastage of phagocytic cells during defence is made good by the primitive syncytial mesenchyme of the pulp, the wastage in lymphocytes is compensated for by proliferation of identical mother cells which form the central core of the lymph follicle. On this assumption, therefore, *the security of the antibody-producing mechanism rests on the power of the undifferentiated mesenchyme to regenerate the essential cellular units of the system.*

In the earlier work on the reticulo-endothelial system dyes and bacteria were usually injected by the intravenous routes. For this reason an erroneous general impression was created and still persists that the system is solely concerned with the removal of foreign particles freely circulating in the general blood stream, and that other tissues not belonging to the system are incapable of reacting in a similar way. Subsequent work has greatly widened this conception. It is now certain that an infinite variety of foreign particles, living or dead, when introduced into any organ or tissue of the body, are dealt with by mesenchymal phagocytic cells present in the tissue itself and forming an integral part of its histological structure. These mononuclear phagocytes or histiocytes, are morphologically and functionally identical with the phagocytes of the reticulo-endothelial organs, but whereas they are present in vast numbers and always mobilised for action in the lymphoid tissues, spleen and marrow, their numbers are scanty and they are difficult to identify in most other resting tissues. Particles of intra-vitam dye introduced into the dermis remain untouched for a variable period but eventually become snowed under by closely packed histiocytes which engulf them. Slowly growing bacteria are dealt with in a similar fashion. *M. Tuberculosis*, for instance, before it begins to disintegrate, and provided the animal is not hypersensitive, inflicts relatively slight damage to the tissues and the cells which eventually deal with it are of local origin. Virulent and rapidly growing streptococci, on the other hand, quickly produce tissue necrosis, and the chemical products liberated when this necrotic tissue autolyses, excite an acute inflammatory reaction and a local accumulation of polymorphonuclear



leucocytes. In this case the phagocytic defence of the tissue is, so to speak, taken out of its hands and largely controlled by the main reticulo-endothelial system, for granular leucocytes are produced in the bone marrow which is one of its largest depots, and this tissue, by rapid proliferation and ripening of its leucoblastic cells, is responsible for maintaining the concentration of granulocytes at the site of an acute infection. When tissue damage is more slowly produced and milder in degree the mesenchymal phagocytic histiocytes provided by the tissue itself are seen to be appreciably larger than granulocytes, have an ovoid weakly staining nucleus containing relatively little chromatin, and copious non-granular cytoplasm. In resting non-reticular tissues these scanty and inconspicuous cells may be recognised by the use of intra-vitam dyes and usually lie in close association with the adventitia of small blood vessels. In some resting tissues, notoriously the great omentum and the subepithelial tissues of the gastro-intestinal and upper respiratory tract, they are far more numerous. In many chronic infections, especially those due to fungi and acid-fast bacilli, the accumulation of these cells in the infected tissue is sufficient to produce conspicuous cellular nodules. On pathological evidence it is quite clear that these cellular masses are produced by continued proliferation by mitosis of fertile mesenchymal cells which were present in the tissue in quite small numbers before it became infected. We must not, however, assume that all the large tissue phagocytes we find in chronic inflammatory foci are fertile cells. We must remember that cells which have become fully differentiated to carry out a specific function probably always become sterile. According to this law we can safely assume that many of the large histiocytic cells present in chronic inflammations and fully exercising their phagocytic function are most unlikely to be fertile. It follows, therefore, that the gigantic cell populations seen in the tissues, and very frequently in lymph nodes in many chronic inflammations, are maintained and can only be increased because, in addition to sterile and fully differentiated mesenchymal phagocytes, they also contain fertile, undifferentiated and non-phagocytic mesenchymal cells. This conclusion is all the more easy of acceptance if we recall that the densely crowded population of sterile polymorphonuclear leucocytes in a focus of acute pyogenic inflammation is maintained by the proliferation of their undifferentiated mesenchymal precursors in the marrow.

In many chronic infections the locally produced histiocytes are accompanied by large numbers of lymphocytes. Their constant presence may have the same significance as the association of tissue phagocyte and lymphocyte as seen in the lymph nodes and may mean that antibodies are elaborated in non-reticular tissues during the course of chronic bacterial inflammation.

The general proposition that *small numbers of highly fertile undifferentiated mesenchymal cells are present in every tissue of the body* was first enunciated by Maximow. He always maintained that such cells could be

recognised in normal tissues but that the investigation of inflamed and healing tissues offered overwhelming evidence of their existence. Maximow devoted many years to the careful investigation of the development of mesenchyme in the embryo and, applying his intimate knowledge to this problem, expanded his original proposition by the assertion that *the fertile undifferentiated mesenchyme richly contained in the lympho-reticular apparatus, but scanty in other situations, was identical with the primitive mesenchyme of the embryo.*

Here we have an assertion which carries certain basic implications and offers a reasonable explanation for a large number of cellular reactions observed in pathological conditions some of which are extremely common. Embryonic mesenchyme during normal development is clearly capable of rapid proliferation. It is the mother tissue of all the common connective tissues—collagen, bone and cartilage and of muscle and adipose tissue. From it are derived all the cells of the blood, all varieties of lymphocyte and every type of phagocyte, the endothelial lining of the blood and lymph vessels, and the primitive cell syncytium lying in a fibrillary reticulum which forms the splenic pulp, the hæmopoietic marrow, the medulla of all lymph nodes and of the sub-epithelial lymphoid aggregates in the gastro-intestinal and respiratory tracts.

Let us accept the proposition that all adult tissues contain embryonic mesenchyme retaining the full histogenetic potency which this tissue exhibits during its normal development, and also agree that it responds to many of the stimuli and insults to which all tissues are exposed under pathological conditions. Under some conditions the response might be solely in the direction of cell multiplication ; with other stimuli the proliferating cells may show a limited degree of differentiation ; with others, proliferation may be over-shadowed by differentiation. In other words, we should find in the first case that the reacting tissue contained a large new population of undifferentiated reticulum cells, many of which would be in mitosis ; in the second and third instances our cell population might contain any of the following cells, all of which owe their origin to embryonic mesenchyme :

1. Fibroblasts producing Fibrocytes.
2. Chondroblasts producing Chondrocytes or Cartilage cells.
3. Osteoblasts producing Osteocytes or Bone Cells.
4. Angioblasts producing Endothelium-lining capillary vessels.
5. Fixed Histiocytes.
6. Free mobile Histiocytes.
7. Lymphoblasts producing Lymphocytes from which Plasma cells probably arise.
8. Monocytes.
9. Myelocytes producing Granulocytes.
10. Erythroblasts producing Erythrocytes.

In other words, a mass of reacting mesenchyme in which the proliferating cells are differentiating may produce a cell population in which one, or any number, or any combination of at least ten histologically recognisable basic cell types are present. We must also concede that in the case of each cytological type the cells may be mature or immature in proportions which vary within wide limits.

If our hypothesis is correct and we can satisfy ourselves that these complex reactions do occur in disease it is quite obvious that they will occur far more frequently and to a far greater degree in the lymph nodes and lymph aggregates and in the spleen and marrow than in other situations.

I should now like to offer you some evidence from pathology which favours the Maximow hypothesis. Before doing so, I must stress the fact that the environment of the reacting mesenchyme may profoundly alter its reaction. Let us consider the cellular events which take place in the gap between the ends of a fractured long bone. The lifeless mass of blood-clot which constitutes the fracture hæmatoma is transformed in a remarkably short time into a temporary splint of living tissue, all of which is cellular mesenchyme. During its early development, it contains angioblasts, fibroblasts, chondroblasts, and osteoblasts, histiocytes removing disintegrating blood pigment and osteoclastic phagocytes removing fragments of dead bone. A little later sprouting capillary blood vessels, fibrous tissue fibrils, cartilage cells and bone cells appear. You may call this hive of cellular multiplication and differentiation the "soft callus" or "granulation tissue" but it possesses to a very striking degree many of the cytopoietic potencies of embryonic mesenchyme and the "blast" cells which are so plentiful in it look remarkably like those seen during normal development. Whilst still in the immature stage these cells are embedded in a soft, watery and structureless gel-like matrix. This becomes finely fibrillated, and its fibrils, being capable of reducing silver salts, become jet black on treatment with silver nitrate. As fibroblasts become clearly recognisable the argyrophil fibrils become thickened, coarsened and strengthened and stain yellow with silver salts. The transformation or replacement of fine argyrophil fibrils by strong, coarse silver-negative fibre is conditioned by the presence in the matrix of adequate amounts of Vitamin C, and this substance appears to be essential for maintaining the strength and integrity of all mesenchymatous inter-cellular material. The matrix in which the osteoblasts and chondroblasts lie is transformed into a rigid gel. By this means osteoblasts produce osteoid tissue; having done so they secrete an enzyme which permeates the rigid gel which surrounds them. This enzyme, known as phosphatase, is capable of catalysing a series of reactions in which organic phosphates, present in all tissues, are dissociated with the liberation of free  $\text{PO}_4^{---}$  ions; according to the law of mass action this results in free precipitation of calcium phosphate. We should take note of this process, because there is enough evidence strongly to suggest that the various types of gelling

and fibrillation which occur in the semi-fluid matrix between mesenchymal cells destined to produce the several varieties of intercellular connective tissue, are due to the secretion by the cells into the intercellular medium of specific catalysts capable of altering its physical state. These considerations lay further emphasis on the properties of primitive mesenchyme. Not only is this remarkable tissue capable of producing a long series of morphologically specific cells but each cell has its own specific bio-chemical function, its macrophages producing antibodies, its red cells carrying oxygen and its osteoblasts secreting phosphatase. A healing fracture then provides an illustration of the cellular multipotency of fertile mesenchyme and the rapidity of formation of soft callus give us some idea how quickly mesenchymal cells divide. I need hardly remind you the angioblastic and fibroblastic mesenchyme which we call granulation tissue teaches us the same lesson. Mesenchyme is sometimes called "packing material." Could any description be more short-sighted?

In long-standing cases of acholuric jaundice, after many years of excessive blood destruction when the hæmopoietic marrow is under great stress and the interior of the skeleton is filled to capacity with deep red proliferating erythroblastic marrow, soft deep red masses having no connection with the bones are sometimes found lying near the necks of the ribs or in close relationship with the renal pelvis. They are composed of proliferating mesenchyme containing many cells which are differentiating to produce erythroblasts, normoblasts and red blood cells. Here we have mesenchyme lying outside the marrow solely engaged in the production of red blood cells. The process, known as extra-medullary hæmopoiesis or myeloid metaplasia, takes place in the lymph nodes, spleen, marrow and liver in all leukæmias, affording an instance in which extra-skeletal mesenchyme differentiates to produce blood cells of the granulocyte series. Extra-medullary hæmopoiesis is not uncommonly found in the walls of calcified arteries as small foci of erythroblastic and leucoblastic marrow occupying the cracks and crannies in the calcified media. In this situation the mysterious influence of environment would appear to play a part.

Almost every variety of cytopoietic multipotency possessed by pathological mesenchyme is found in the reticuloses. In one of these, histiocytic medullary reticulosis, the enlargement of lymph nodes is entirely due to proliferation of their mesenchyme accompanied by diffuse widespread differentiation to produce a large new population of phagocytic histiocytes, many of which ingest red blood cells and subject them to intracellular lysis. The disease quickly becomes systematised in the spleen and marrow and the red cell destruction is severe enough to produce jaundice and rapidly developing anæmia. In lymphoid follicular reticulosis, on the other hand, the process of differentiation is more complex. The lymph nodes and spleen show striking degrees of progressive enlargement entirely due to the new formation of enormous numbers of abnormally large lymph follicles, each of which shows a pale centre of large

primitive lymphoblastic cells and a peripheral zone of closely packed small lymphocytes (see Figures 6 and 7). Differentiation in this disease has reached the stage in which organised histological structures having a specific architecture are produced, the giant follicles being almost identical with the "germinal centres" or follicles of the cortical portion of a normal lymph node.

In Hodgkin's disease, growth and differentiation are present side by side in proportions which vary considerably during the evolution of the disease in any one site. Proliferation is marked in the early stages but differentiation is always present. The well-organised cortical and medullary architecture of the lymph node is quite quickly wiped out, the germinal centres disappear and sinuses are no longer recognisable. Sheets of proliferating cells replace them. The nuclei of these cells are large, their cytoplasm scanty, and an appreciable proportion are in mitosis or pre-mitosis so that there is considerable anisocytosis. These cells resemble those of the primitive syncytial mesenchyme present in small amounts in the cellular medullary pulp of any normal resting lymph node. Multipolar mitosis is frequently encountered in these cells and binucleate cells are common, their double nuclei lying side by side giving the impression that one is the mirror-image of the other. Other giant cells have from three to six nuclei which almost fill the cell. These were first recognised and described by Greenfield in 1878 and further described by Andrewes, Sternberg and Dorothy Reed. Even in the early proliferative phase it is always possible to find clear evidence of cell differentiation in the shape of easily recognisable fibroblasts producing fibroglia and collagen. Experience teaches us that it is unwise to make a histological diagnosis of Hodgkin's disease unless this fibroblastic differentiation can be clearly made out, and in this connection it is essential to realise that the fibroblasts are not derived from or have any connection with the fibrous bands or trabeculae which form the gross fibrous skeleton of the normal node, but arise in a diffuse fashion in the midst of the newly formed undifferentiated cells. As the disease progresses proliferation gives way to differentiation and the end-result is fibrosis with deposition of a gross excess of collagen. Not so constantly, but very frequently, it is possible to identify another variety of cell differentiation in the form of isolated clumps and masses of granular leucocytes, the majority of which have large eosinophil granules. During her careful investigation of lymphadenoma, Pullinger was able to demonstrate that these cells are often accompanied by neutrophil polymorphonuclear leucocytes and a small but appreciable number of granular myelocytes. In this disease, therefore, we find free proliferation at the level of the undifferentiated mesenchymal cell accounting for most of the swelling of the lymph node in the early stages. This is accompanied by differentiation along two lines, one giving rise to the production of fibre-forming fibroblasts, the other to myelocytes producing granular leucocytes. Hodgkin's disease fulfils all the essential conditions which justify its inclusion in the reticulosis group. In the first place there is never

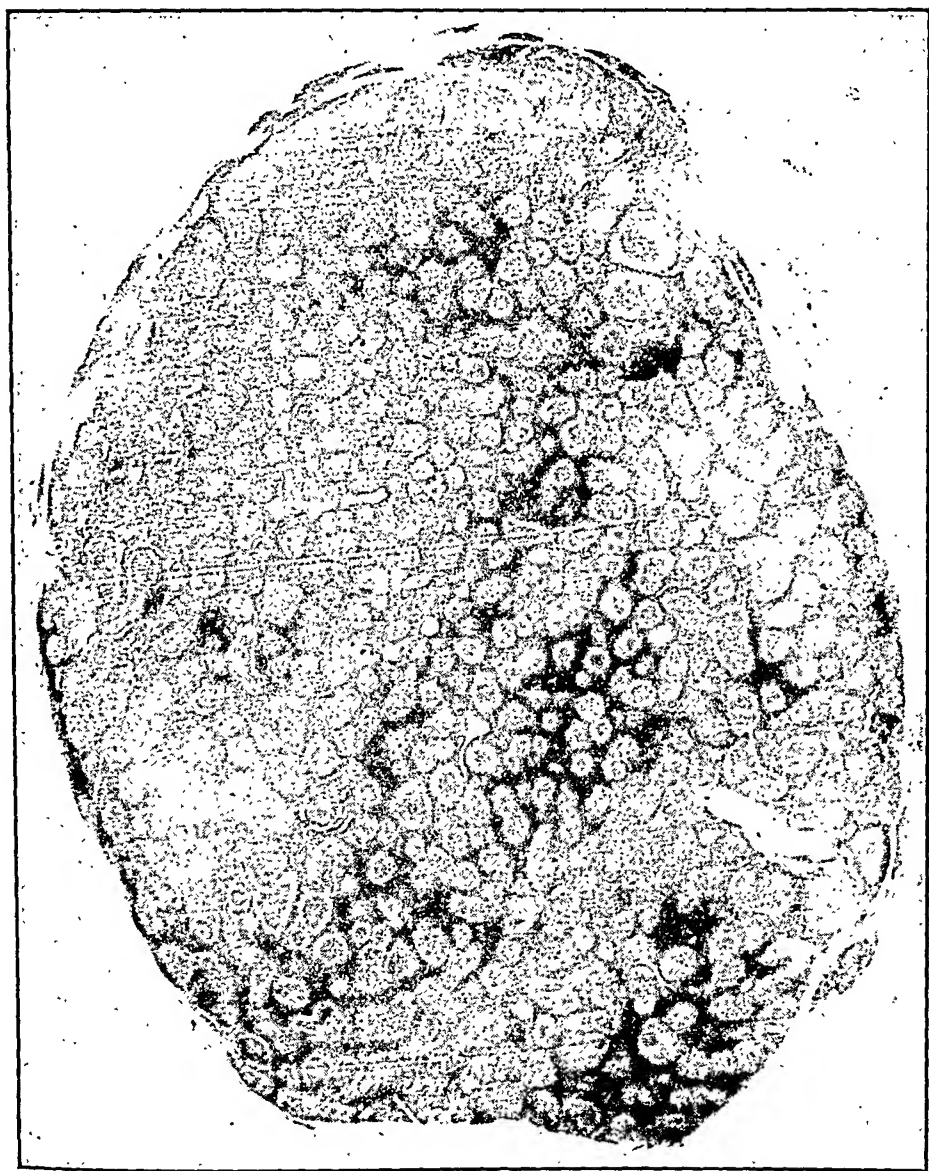


Fig. 6. Lymphoid Follicular Reticulosis. ("Follicular Lymphoblastoma.")  
Low power view of the whole of a cervical lymph node. The pulp of the greatly enlarged spleen in this case had an almost identical structure.

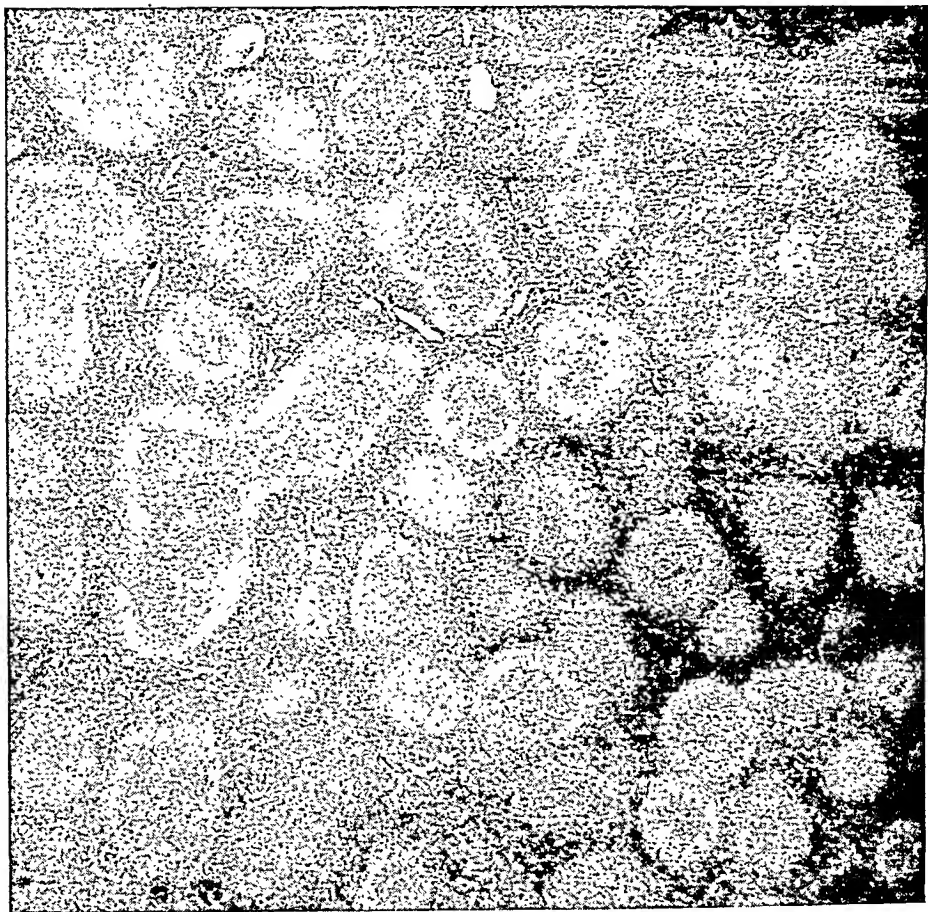


Fig. 7. Lymphoid Follicular Reticulosis. High power view of Fig. 6.

at any stage any sign of eruption of the proliferating cells through the gland capsule with invasion of surrounding tissues. Secondly, it shows a remarkable tendency to become generalised in the organs of the lymphoreticular apparatus ; thirdly, the growth is invariably progressive.

To appreciate the maximum growth capacity of the undifferentiated mesenchyme of a lymph node under a pathological stimulus, we must turn to the several varieties of primary new growths which occur in the deep and superficial lymph nodes, in the sub-epithelial gastro-intestinal and upper respiratory lymph aggregates, and in the skeletal marrow. Common to all these diseases is anaplastic, progressive and destructive cell growth. The vast new populations of young cells produced usually bear some resemblance, sometimes a very close resemblance, to primitive mesenchyme. They may have a syncytial arrangement as in embryonic mesenchyme ; they may produce copious argyrophil fibrils, or may furnish a close copy of lymphoblastic mesenchyme with free or limited production of lymphocytes.

In conclusion I should like to put forward the following generalisations for your consideration :

1. Undifferentiated mesenchymal cells are present in all tissues, but are richly contained in lymph nodes, and the physiological cytopoietic multipotency of these cells explains many of the histological changes found in the lymphadenopathies.
2. The changes found in lymph nodes in disease must be related to those which occur in the lympho-reticular apparatus of which which they are a part.
3. The organs of this system produce antibodies to bacterial antigens which are taken up out of the blood by their phagocytic cells. There is enough experimental evidence strongly to suggest that a lymph node reacting to local lymph-born antigens is also capable of producing antibodies. In this process the lymphocyte probably plays a major rôle. If this is confirmed it will be possible to establish a basic functional relationship between the lymphoid follicles of lymphoid tissue and the cellular filtering mechanism which forms its pulp.



## ALBAN HENRY GRIFFITHS DORAN (1849-1927)

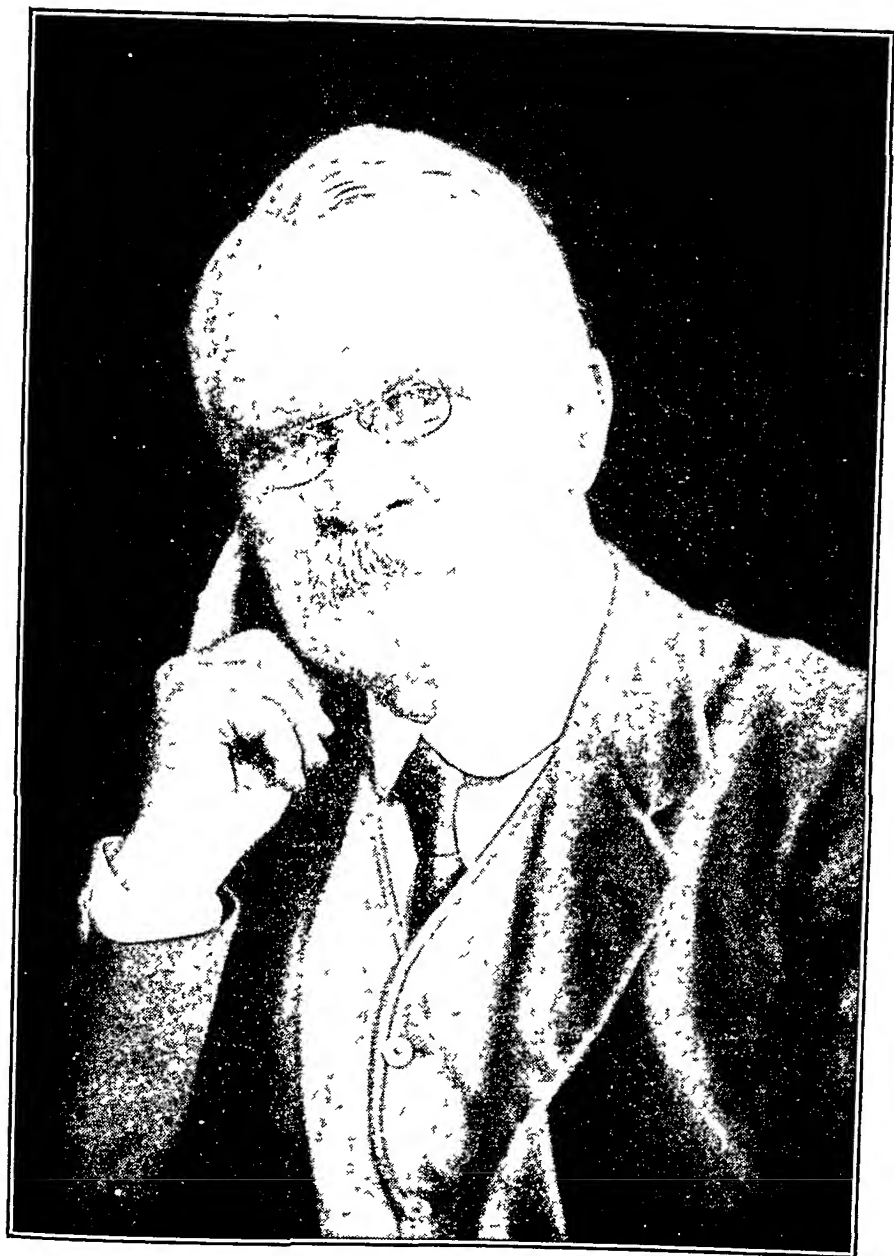
by

W. R. Bett, M.R.C.S.

THE CENTENARY OF the birth of "Dear Old Doran" is an event worthy of notice in the *Annals of the Royal College of Surgeons of England*, for his connection with the College extended over more than half a century.

'Alban Doran was born on 12th February, 1849, at 4, Pembroke Terrace, Kensington. He was the only son of John Doran, Ph.D., F.S.A., editor of the *Athenæum* and of *Notes and Queries*, and author of *Their Majesties' Servants*, who numbered among his friends Thackeray, Douglas Jerrold, William Powell Frith, Sir Henry Thompson and Luther Holden. After attending a private school at Barnes, Alban Doran at the age of 18 became a medical student at St. Bartholomew's Hospital, where he won scholarships and prizes with annual regularity, took the M.R.C.S., L.S.A., in 1871, and was appointed house-surgeon to Luther Holden in 1871 and 1873, and assistant-demonstrator of anatomy. His long and devoted work for the College, of which he became a Fellow in 1875, was begun in 1873, when he was appointed anatomical assistant to Sir William Flower. Acting as Museum Secretary, he came into contact with Owen, Huxley and Virchow. It was while helping Flower in his work on craniometry that his interest was aroused in the middle ear of mammals. He made the remarkable "Doran Collection of Ear Bones" from the mammalian skulls in the Museum and published an equally remarkable monograph on the subject, with engravings by Charles Berjeau, in the *Transactions of the Linnean Society* (1878). Up to the time of his death he delighted in any reference to this paper in the writings of later investigators. In the College Library is preserved a letter written to Doran by the great anatomist Joseph Hyrtl, dated 30th November, 1878, in which, in a curious mixture of English and German, he refers to Doran's "memorable work, a model of anatomical industry, exactness and learning. Comparative anatomical morphology will for ever boast of your investigation of such an arduous and hitherto almost neglected department of osteology." He ends on a pathetic note: "I am almost blind. This will excuse the laconical form of my letter." Fifty years later the recipient of this letter was almost blind himself.

In 1877 Doran succeeded Sir James Goodhart as Pathological Assistant to the Museum. Goodhart had just finished a descriptive catalogue of the pathology of the viscera, but when the proofs were laid before the Council in 1880, it was resolved to prepare a complete second edition of the Pathological Catalogue, the first having been issued in 1846. Sir James Paget, asked to undertake this task, assisted by Goodhart and Doran, attended the Museum punctually at three o'clock every Friday. All three compilers inspected every specimen in the General Series. While Goodhart was made responsible for the internal viscera, and Doran for the diseases of the ovaries, uterus, etc., Paget and Doran went



*Photo by Elliot and Fry, Ltd.*  
Alban Henry Griffiths Doran.

through the Surgical Series together. Paget did not like having specimens placed on a table, so that he and his assistants might sit down and pursue their investigations in comfort. He would stand up for a couple of hours, studying the specimens on the rail-cases in the galleries and showing no signs of fatigue. When the proofs were ready, he scrutinized every description prepared by Doran, comparing it critically with the specimen in question. He greatly admired the preparations demonstrating Spencer Wells's skill and expressed open indignation at the "faked" statistics of many other gynæcologists. Concerning two flagrant cases, he remarked to Doran: "Well, after all, they may be two of those men who would not lie for all the world, yet cannot for the life of them tell the truth."

In 1877 Doran was elected Assistant Surgeon to the Samaritan Free Hospital for Women, remaining on the Staff for more than 30 years. In those early days it was his ambition to become a surgeon with a large gynæcological practice, but he had no surgical hands, though he made a reputation as an ovariologist, and certain eccentricities of movement and expression hampered his success as a fashionable consultant. The chief interest of his *Handbook of Gynæcological Operations* (1887) to Sir John Bland-Sutton was its critical care of the orthography of gynæcological terms and the names of instruments.

Compelled by failing sight to abandon private practice in 1909, Doran devoted much of his time to the Museum, working with Samuel George Shattock in re-arranging the obstetrical and gynæcological specimens, and with John Davis Barris in mounting a collection of normal and deformed pelves. When the Obstetrical Society, of which he was President in 1899, was absorbed by the Royal Society of Medicine, Doran made himself responsible for the transfer of its museum as a loan-collection to the College. The task of compiling a catalogue of its obstetrical and gynæcological instruments was a tremendous one, calling for wide and accurate scholarship and religious attention to minutiae. But these were qualities which he possessed in abundance and never displayed to greater advantage. His knowledge was encyclopædic, his memory little short of miraculous.

While in his 77th year, Doran still attended the Museum on two days in each week, in order to keep the catalogue of surgical instruments up to date. In June 1927 he paid his last visit to his beloved College, accompanied by a nurse, for he was nearly blind. Taken to the Instruments Room, the old man became bright and cheerful, and he was just able to distinguish some of the exhibits he had described with such scholarly care.

He underwent an operation for acute glaucoma in St. Bartholomew's Hospital, but fainted either during or just after it and died in the ophthalmic ward on the 23rd August, 1927.

An enthusiastic Shakespearian scholar, Doran delivered a memorable annual oration before the Medical Society of London on "Shakespeare

## ELECTION OF PRESIDENT AND VICE-PRESIDENTS

and the Medical Society," and he contributed the article on medicine to *Shakespeare's England* in the tercentenary year.

In his old age he was a benevolent, white-haired, bearded figure. A marvellous talker with a delightful sense of humour, he was most approachable and liked the company of the young. He had the habit of talking to himself, when he scarcely minced words, but would suddenly stop and say: "Now, Doran, be careful, or you'll start swearing in a minute."

I had the good fortune to meet Alban Doran for the first time as a medical student in 1924, when I was collecting material for a paper on Sir James Paget. He was most accessible, most informative, and most charming, and some of his reminiscences are recorded in this centennial tribute.

### ELECTION TO COUNCIL—7th JULY, 1949

Mr. A. Dickson Wright, Sir Stanford Cade and Mr. Digby Chamberlain were elected Members of the Council for the period of eight years.

1,791 Fellows voted: in addition 12 votes were found to be invalid, and three arrived too late.

The result of the Poll was as follows:

Candidates	Votes	Plumpers
DIGBY CHAMBERLAIN .. .. .	726	133
SIR STANFORD CADE, K.B.E., C.B. .. .. .	632	42
ARTHUR DICKSON WRIGHT .. .. .	556	26
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### ELECTION OF PRESIDENT AND VICE-PRESIDENTS—14th JULY, 1949

Sir Cecil Wakeley was elected President. Sir Harry Platt and Mr. Ernest Finch were elected Vice-Presidents.

# FIBRO-FATTY TISSUE AND ITS RELATION TO CERTAIN "RHEUMATIC" SYNDROMES

Hunterian Lecture delivered at the Royal College of Surgeons of England

on

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by

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## INTRODUCTION

IF THE OBSERVATIONS I put before you to-day are correct ones, we are now in a position to turn over a fresh page so far as our conception of certain of the so-called rheumatic syndromes is concerned. I am not, I fear, in a position to do much more than to write the chapter heading for this new page; it seems to me, however, that this new chapter will be worth writing when adequate material is forthcoming.

It is generally agreed that much of the pathology described for the chronic rheumatic diseases is speculative rather than factual. Biopsy does not seem to confirm the current impression that muscle or fibrous tissues are generally the seat of cellular change in non-articular rheumatism—nor, indeed, that inflammation is the underlying pathology.

So far as aetiology is concerned, I suggest that bacteriology has had its day, and that the day of endocrinology, and perhaps genetics, is dawning. The therapeutic witch-hunt for focal sepsis is slackening—we need an alternative line of thought.

Pathologically, the contribution I wish to make is simple, but I believe fairly far-reaching in this field. There is a third tissue also of mesodermal origin, namely fat, which has seldom been considered in this connection, but which appears to be quite commonly subject to pathological variations which may cause symptoms which are labelled "rheumatic." Fatty tissue is widely distributed and constitutes nearly 20 per cent. of the body weight. It appears to be functional as well as protective, and this being so it would be strange if its functions were not sometimes disordered. One of these functions appears to be concerned with water storage (the most striking example of this is perhaps seen in the behaviour of the camel's hump). It has been established of recent years by Bishop and others that human fat may retain water to a pathological degree in certain disorders. It would seem to be some derangement of this normal function of water storage which underlies the syndromes discussed in this lecture.

## FIBROSITIS

Fibrositis as a clinical entity has for many years past been accepted in this country although its pathological foundations are, as has been mentioned, slender resting almost entirely upon the theories of Gowers (1904); the equally unconfirmed histological studies of Stockman early in the present century (1920); and the suggestion of Elliot (1944) regarding muscle spasm as a cause. Stockman defined fibrositis as "a

condition of chronic inflammation of the white fibrous tissue of the fascial aponeurosis, sheaths of muscles and nerves, ligaments, tendons, periosteum, and subcutaneous tissues, occurring in all parts of the body and giving rise to pain, aching, stiffness and other symptoms, the result of preceding general infections or local inflammations or injuries." It is now generally defined less comprehensively as an idiopathic disorder of the soft tissues chiefly characterised by pain and tenderness which may be local, widespread or referred, and is often associated with muscular spasm.

*Nature of the pain in fibrositis.*—It was only comparatively recently that Lewis and Kellgren and others pointed out that the pain in fibrositis generally has its origin in certain focal points from which the more general subjective pain complained of by the sufferer is referred according to a segmental plan. This referred pain may appear to be situated at a considerable distance from its real origin. A good example is to be seen in those cases of sciatica not due to a disc mechanism, in which the focal point of pain—the "trigger point"—may be found in the region of the iliac crest, or even in the lumbar region. These trigger points, which when they are palpable are termed "fibrositic nodules," are definite objective clinical entities in so far that when they are found by the examining finger the patient winces involuntarily. They are not merely tender spots, which are also commonly found but they are specific points at which real pain is produced, and from which the more general pain can be referred by fairly light pressure. The existence of these trigger points is now well recognised in view of the therapeutic success which often attends their injection with local anæsthetics in saline. Palpable nodules which are not tender are not infrequently found, but do not appear to be significant from a clinical point of view.

*Classification of fibrositis.*—Himsworth in his Oliver-Sharpey lectures (1949) emphasised the liberation of medical thought which has resulted from the substitution of syndromes for "disease entities" as units of illness. The syndrome has its philosophical basis in a chain of physiological processes, interference with which at any point produces the same impairment of bodily function. He points out that the same syndrome may thus arise from different causes. This conception inspires a much more catholic concept of ætiology which is no doubt fully applicable to the field of "rheumatism" in all its forms. It must not, therefore, be assumed that the conclusions put forward in this lecture are thought to explain more than a proportion of cases. It will also be apparent that an ætiological classification will be unlikely of attainment in this field.

It would seem that the only objective sign of the disorder lies in these localized trigger points which are moreover sometimes palpable in the form of nodules; it seems reasonable therefore to attempt to classify fibrositis according to the anatomical nature of the nodule, where this is known or strongly suspected. Very little biopsy or other work of this nature has been done as yet, and the accompanying table based upon this objective must be regarded as being very provisional. It seems possible,

however, that some form of classification such as that which follows, might ultimately prove useful.

“ FIBROSITIS ”

Nature of Pain	Site	Clinical Finding	Morbid Anatomy	Cause
1. Focal ..	tendon or aponeurosis	nodule, small and hard	fibrous	trauma, rheumatic fever
2. Focal ..	lumbar or gluteal	larger nodule	fibro-fatty	œdematous changes
3. Focal ..	on muscle belly	smallish elongated “ nodule ”	local spasm of muscle fibres	irritative focus in neural segment
4. Diffuse ..	whole muscle group	muscle tenderness	unknown	toxæmia
5. Diffuse ..	many muscle groups	spasm	chronic muscular fatigue	psycho-neurosis
6. Diffuse (sometimes local)	subcutaneous tissues	panniculitis, tender fat deposits	abnormal œdematous deep fat	endocrine

Fig. 1. An attempt to classify non-articular rheumatism according to the anatomical nature of the source of pain.

*Ætiology of trigger points and nodules.*—It was observed (1941) that the pain in the back which accompanies most pyrexial illnesses is of the same nature and pattern as in fibrositis. It was shown, moreover, that although the pain disappears with the cessation of pyrexia, the tender trigger point will persist in a proportion of cases often for very long periods, unknown to the patient. These trigger points can be reactivated by a recurrence of pyrexia, even if this be due to a different cause. It is suggested, therefore, that the tissues in which trigger points and nodules subsequently occur in the course of fibrositis may sometimes have been “ sensitized ” earlier in life in the course of an attack of influenza or one of the exanthemata. The nature of the lesion may be a recurrent œdema painfully distending certain fat lobules in the deep subcutaneous tissues. It has also seemed certain that trauma, and probably also the direct action of cold, can be causative of similar lesions or at least precipitate their development. No evidence of the direct causative effect of focal infection has been established.

**Fibrositis due to œdematous changes in the fibro-fatty tissues in certain sites**

*Method of investigation.*—The frequency of the occurrence of fibrositic pain of the lower back in otherwise healthy young soldiers first stimulated our interest in this matter. As a first step, exact measurements were taken of the site of these trigger points or nodules in a large number of sufferers and a pain chart was plotted. The back of every patient who died in hospital was systematically dissected and special reference was made to

these areas. As the result of this, and of many subsequent clinical observations and biopsies, certain conclusions regarding "fibrositis" and similar conditions in this and other regions of the body have been arrived at, many of which are embodied in this paper. The pain chart which evolved as the result of plotting the site of the trigger points or painful nodules in our series of cases of lumbar fibrositis as already mentioned, was found to outline the edge of the erector spinæ muscles, the crest of the iliac bones, and the sacro-iliac joints. It was later found that this chart also corresponded with areas in which residual fat occurred, even in cases dead with the grossest forms of cachexia.

As no evidence of pathological change could be found in fibrous tissue or muscle in biopsy material, we decided to examine the deeper layers of fat which constituted the remaining tissue in the neighbourhood of the trigger points—notwithstanding the usual assumption that no pathology of interest normally affects this type of tissue. We were lucky in our first case in that we noticed a curious herniation of a large lobule of distended fat through a defect in the deep fascia. In a later biopsy of an easily felt and tender nodule, from which widespread pain was being referred, we discovered by cautious dissection that the nodule in this case was an œdematous-looking node of fatty tissue lying amongst superficial fat of the upper buttock, but with a pedicle which could be traced down to the layer of fat lying beneath the deep fascia.

*Fatty structures as a site for painful lesions.*—In our original paper (1944) we described the areas of fat in which painful "fibrositic" lesions occurred as being in the main "residual," in the sense that lobulated fat remains in these areas even when it disappears from other areas as the result of extreme cachexia. The colour of this residual fat in such cases we noted as being often darker or pinker than ordinary fat. In two cases we were able after death to trace the pedicle of a superficial fat hernia down to the para-nephric fat mass. These observations suggested to us that the areas of fat liable to be affected, at any rate in the lumbar region, might bear some relationship developmentally to the primitive renal fat gland round which from a comparatively early period of embryonic development fat congregates in closely lobulated clumps, which in rats (according to Hammar) is also of a darker colour than normal. The well-marked area of residual fat which lines the rim of the ilium may not be covered by this hypothesis, although another primitive fat-organ is described in the outer groin by some textbooks. The largest of these fat-organs is said to be situated between the scapulæ—a position which seems to correspond with that of our dorsal fat pad.

*Normal anatomical disposition of fat.*—Not much information is to be found on this subject in most anatomical textbooks. Subcutaneous fat exists very generally throughout the body although its distribution is not uniform. In certain situations it collects more abundantly. Here it forms a considerable layer beneath the reticular layer of the corium where it is laid down in the subcutaneous areolar tissue—*panniculus adiposus*.



This areolar tissue forms a thin, indistensible fibrous capsule round the large lobules, where the fat is lobulated. The lymphatics serving fat accompany the blood vessels in very close relationship as they enter the lobule. There are numerous sensory nerves to the blood vessels, and possibly to other structures in the lobules, and sympathetic nerve fibres which run to the fat cells control the function of storage and yielding. Where the skin is thicker and less movable, the reticular layer is fixed to the deep fascia by numerous stout fibrous bands (*retinacular cutis*), the space between being filled with firm fat-clusters. This formation normally occurs mostly on the posterior aspects of the trunk and the upper and outer aspects of the limbs.

*Pathological herniation of fat lobules.*—From the brief account which has so far been given it will appear that what pass as fibrositic trigger points can often be shown to be related topographically in the lumbo-sacral region with the basic fat pattern. Where these tender points were surgically explored, herniation of distended fat lobules through deficiencies in their investing fibrous covering was frequently found. Removal or disruption of these herniæ in such cases provided lasting relief from pain. Histological examination of the material removed has shown in practically every case nothing but normal fat tissue distended with œdematous fluid; suggesting that the cause of this œdema is not inflammatory.

In the lumbo-sacral region the fat herniæ seen so far have been of three types (1944): (a) pedunculated, (b) non-pedunculated, and (c) foraminal.

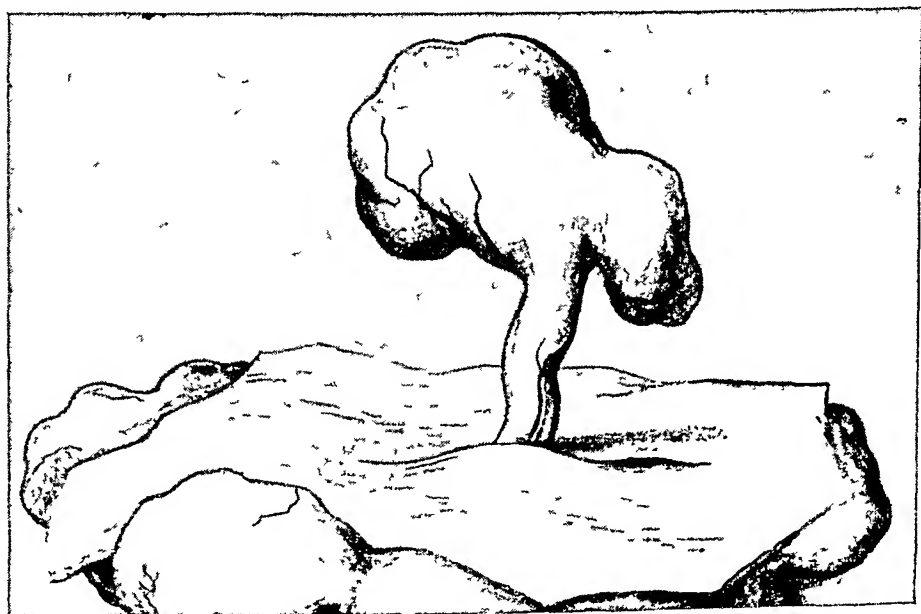


Fig. 2. Fatty Hernia : Pedunculated type.

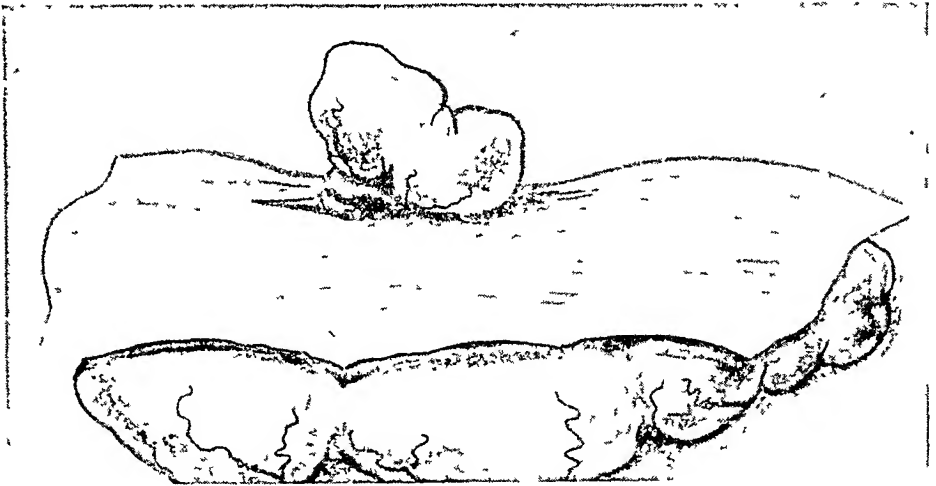


Fig. 3. Fatty Hernia : Non-Pedunculated type.

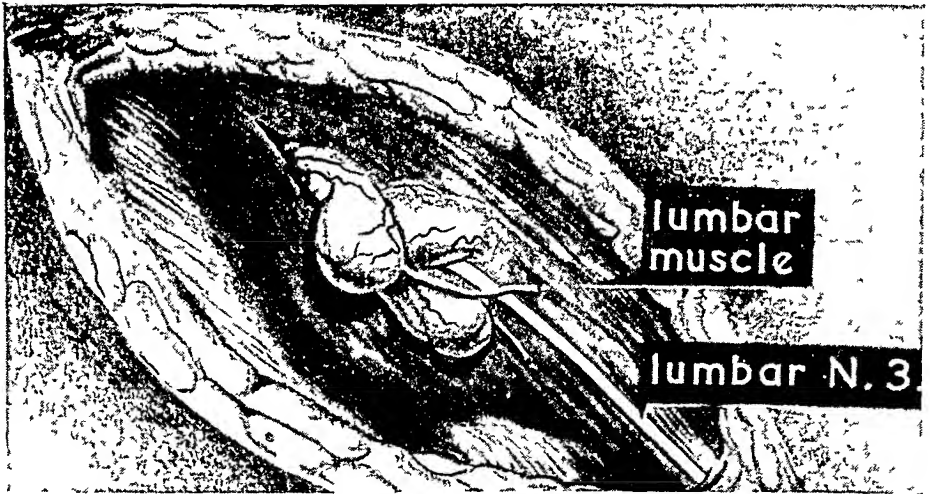


Fig. 4. Fatty Hernia : Foraminal type.

The first two are self-explanatory, the herniation occurring from the deeper layer of fat through a fascial covering or layer into a more superficial layer. The foraminal herniæ occur along the foramina which exist in the deep fascia of the sacrospinalis muscles along which pass the lateral branches of the posterior primary divisions of the first, second and third lumbar nerves together with a small artery and vein.

Twenty-two selected case histories from our series have been published (1944 : 1947) in which removal of a fat hernia of one of these types resulted in a permanent cure of the pain, and many subsequent unpublished cases have been investigated with similar findings and results.

Hertz (1947) working in Cleveland has confirmed this work and has published two further series of successful cases.

### Lesions other than herniation occurring in fat of normal distribution

#### *Upper dorsal region*

The skin is normally six to eight times thicker in this situation than in most parts of the body, and islands of fat may be found actually in the reticular layer of the corium of patients suffering with panniculitis. In the upper back the fibrous projections between the corium and the deep fascia normally form a series of honeycombe-like compartments which are filled with vascular fat. The axes of these "cells" is found to be roughly parallel, with the tension (cleavage) lines of Langer. This structure is particularly noticeable in the upper back area and we have called this diamond-shaped area the "dorsal fat-pad." It is one of the common sites of "fibrositic" pain, and its area corresponds fairly accurately with that of the trapezius muscle which lies beneath it. When painful nodules are palpable, as is commonly the case in "fibrositis" of this region, they are seldom fibrous in nature. Biopsy will generally disclose the nodule to consist in the fatty contents of one or more of these compartments, swollen and under tension. Tension is shown by the fact that if the incision is made at right angles to the lines of tension in the skin the wound will gape and the lobule will be seen to present above its surface. It is also shown

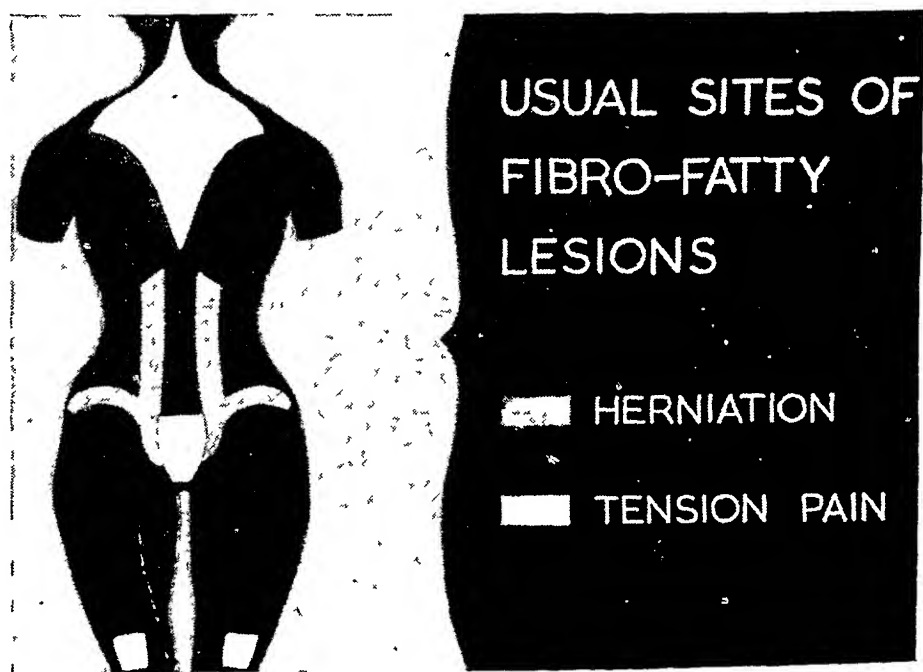


Fig. 5.

by the "peu d'orange" appearance if the skin and subcutaneous tissues of an affected area are compressed laterally. Negative evidence of this is afforded by the well-attested observation that palpable nodules of this type can be "rubbed away" by means of deep massage; a fact that could not be rationalized if they were formed of solid material such as fibrous tissue. Herniation of these lobules into adjoining compartments has been observed but is uncommon owing to the density of their walls.

### *Peri-articular fat pads*

It does not appear to be generally appreciated amongst clinicians that localized collections of fat are to be found normally in association with certain joints, particularly the knees and ankles and that these may become painful without the joint itself being necessarily affected. When this occurs an irresponsible diagnosis of arthritis is often made as the result of insufficient examination.

(a) *The patella fat pads.*—A normal intracapsular fat pad is situated between the joint and the patella. This is well recognized by anatomists and surgeons. These infra-patella pads will often become tender and painful without the joint itself being affected; this is particularly so around the time of the menopause. It is this lesion which commonly gives rise to the sensation of grating on movement which is sometimes considered to imply that arthritis is present. A fold called the infra-patella synovial fold extends posteriorly from the apex of each fat pad to be attached to the femur inside the joint cavity. No doubt in certain cases if this is also affected, intra-articular function will to some extent be deranged.

(b) *The "popliteal fat pad."*—This has not so far as I am aware been described as a separate entity. It is, nonetheless, present in more than 80 per cent. of normal people over 40 years of age. When it attracts notice by enlarging and becoming tender it is often wrongly described as a bursal

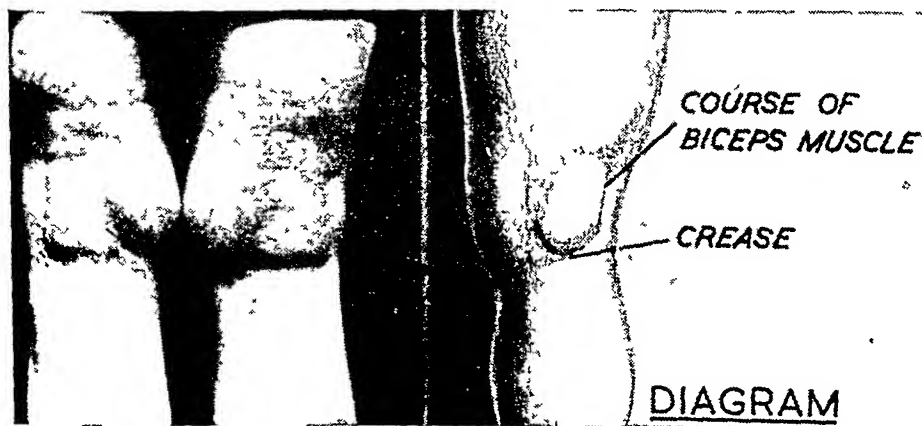


Fig 6. The Popliteal fat pads. Normal Structures which generally enlarge when painful. Often mistaken for Bursæ.



Fig. 7. The Sacral fat pad. Present in about 10% of normal subjects.

enlargement. It is sharply limited as to its lower margin by the upper crease of the popliteal skin its outer border lies roughly parallel with the course of the semi-membranosis muscle. Its upper border, when the pad is large, is delineated by another crease which develops in these circumstances. The inner border lies to the outer aspect of the mid-line of the popliteal space. This fat pad lies between the superficial and deep layers of the fascia covering the popliteal space. When large it distends the skin, although the cause of pain and tenderness appears to lie rather in the distension of the fat itself. In these circumstances, however, full flexion of the knee joint by compressing the fat pad may give rise to pain; and so again to a mistaken diagnosis of arthritis.

#### *The sacral fat pad*

This is a structure which can be observed in about 10 per cent. of normal persons. In structure it is very similar to the dorsal fat pad. It is rather smaller than the sacrum, but is of the same shape and lies over it. It sometimes enlarges painfully as an isolated phenomenon, but more frequently in association with a general condition of panniculitis, either with or without obesity.

Two other small fat pads exist in many normal persons and in all who are obese. I can find no published description of them, however. The first is situated over the dorsal surface of the basal phalanx of the great toe. The so-called "male hairs" described by Wood Jones spring from its surface. It seems to be designed to buffer the strong action between the tendon extensor hallucis longus and the skin. It is seldom of clinical significance although its enlargement greatly contributes to the shiny swelling of the skin in this region in cases of acute and sub-acute gout. The other fat pads which seem to be of some significance in so far as they often become swollen and painful in obese persons, are situated at the

ankle joint. Medially there is one between the malleolus and the heel, roughly over the flexor retinaculum; whilst on the fibular side one lies over the stem of the inferior extensor retinaculum. A further fat pad sometimes develops over the adductor tendons of the thigh at their pubic origin. It is rather doubtful, however, whether this can be considered to be of normal occurrence. They always develop in cases of obesity and may be very painful.

*Clinical effect of altering volume and distribution of body fluids*

If the views which have been propounded are correct regarding the role of increased fluid tension in certain tissues causing pain, it should prove possible to relieve the pain by reversing this process. An experiment was accordingly planned with Pugh (1945) whereby 22 cases of fibrositis in which we believed that the pain might be of this type, were selected. In these patients we induced the state of clinical dehydration; at which point we added electrolyte to the extra-cellular fluid to increase its osmotic pressure. Since the cell membranes are impermeable to sodium and chloride, intracellular dehydration would result.

*The method* of achieving this was to restrict the fluid intake of these patients for 36 hours to about eight ounces (225 c.cm.). After this, for a further 24 hours, they were allowed neither food nor drink, and their fluid output was increased by the administration of sodium sulphate, half ounce at hourly intervals for six doses. The process of dehydration could be followed by noting the daily loss of weight which varied between 1-3.5 kgm. This preliminary stage of dehydration was followed by an intravenous injection of 50 c.cm. of 30 per cent. sodium chloride (15g.) into a vein. Immediately after this injection the patient was allowed to drink four ounces of tea to mitigate thirst. Apart from this no fluid was permitted for four hours; after which no further limitation was imposed and the patient was encouraged to get up and about.

*The clinical result* of intracellular dehydration in this group was that of the 22 patients submitted, 13 were rendered completely free of pain for variable periods. It was thought that this experiment confirmed other evidence as to the nature of the mechanism of the pain suffered in the successful cases.

### PANNICULITIS

*Relationship of panniculitis with fibrositis.*—According to Stockman pain of unknown origin occurring in mesodermal tissue, which he believed (as is indicated by his nomenclature) was always due to inflammation of the white fibrous tissues, is covered by the generic term fibrositis. Pain, which has been described above as occurring from the distension in normally situated subcutaneous fat lobules, can also therefore conveniently be classified under this heading. Where the pain of this type occurs in abnormally deposited fat, however, it will be referred to as panniculitis. The condition was described by Stockman (1911) and also by Telling. It was defined by the former as being fibrosis of the deep

subcutaneous tissues, or more specifically as "a chronic inflammation of the areolar tissue of the panniculus adiposus, including the small nerves and blood vessels." Although he recognized the presence of excessive fat locally he considered this to be the result of the inflammation and did not recognize that it had any association with the pain.

Panniculitis is a common condition which is insufficiently recognized as a cause for pain which is not infrequently labelled as "psychogenic." Our investigations have shown no single instance histologically of an inflammatory reaction having occurred, and we believe that the pain in this condition originates as the result of œdema, and consequently distension, of lobules of the abnormal fat deposits. Panniculitis can best be considered in relationship to those regions of the body in which it is most commonly encountered; namely, the upper dorsal region, the upper and outer aspects of the limbs, around certain joints—especially the knees, elbows and ankles, and some other sites. Panniculitis is often associated with general obesity. Even in cases showing this association the sites of pain generally remain confined to the regions in which pain is situated in cases not so complicated. This localization of the pain in cases of general obesity may be due to the less lobulated nature of the fat which is laid down elsewhere and also to the fact that in other sites, such as the abdominal wall, no fibrous fascia or capsule is present to limit the distension of the fat if it becomes œdematous. Herniation of fat lobules is common in association with obesity.

*Adiposis dolorosa.*—Although adiposis dolorosa would seem to differ from the preceding syndrome merely in degree, it does show more generalized areas of pain. The nodular feel of the fat deposits, the fluctuation in the sites of pain, and the histological findings however suggest that the underlying cause of the pain may be the same as in the preceding syndromes; namely, a shifting non-inflammatory œdema affecting the pathological fat deposits. In this connection it is interesting to note in Dercum's original description (1892) "occasionally very severe paroxysms of pain occurred, and these were co-incident with temporary swelling and hardening of the fat masses."

*Panniculitis of the upper dorsal region.*—The dorsal fat pad which has been described as the seat of local lesions in fibrositis, is more generally involved in cases of panniculitis. The tissues are sometimes excessively thickened and the subcutaneous tissues cannot be lifted between the finger and thumb. It is sometimes the only region involved in this process in which case the condition tends to be concentrated round the base of the cervical spine in what the Americans have termed the "buffalo bump."

*Panniculitis of the upper and outer aspects of the limbs.*—Tender nodules not infrequently form along the upper and outer aspects of the thighs, often in association with enlargement of the peri-articular fat pads of the knee which have been discussed above. Pain due to this cause is generally diagnosed as "fibrositis." A few biopsies and dissections have been made to study the method of formation of nodules in this site.

The usual situation of these localized collections of fat is in the panniculus adiposus where certain portions of the areolar tissue seem to become more heavily charged with fat than do others. These portions appear to be more closely lobulated and independent of the average layer of fat at this level, although lying in it, and give the appearance of being small independent "mesenteries" each with its own blood and lymphatic supply. There is also a large potential space between the superficial and deep layers of the fascia which overlies the fascia lata of the thighs, and fat nodules sometimes form also in this space. In cases where these collections become painful in this situation, it is found that they have become circumscribed by adhesions which appear to prevent lateral extension of the fat mass. The pain is presumably due in such cases to attempted distension of the unyielding fascial walls. The cause of these limiting adhesions is unknown, it may be traumatic, but since their occurrence appears to be related in many cases to the menopause they may result from a drying-up of the normal lubricating fluid of the fascia. No detailed investigations have yet been carried out to investigate similar conditions in the region of the upper arm or round the elbow joint, where panniculitis is also commonly found.

*Knee joint.*—An abnormal fat pad develops over the inner aspect of the knee joints as a menopausal manifestation, and perhaps precursor of ultimate osteoarthritis. It also occurs as a prominent feature of general obesity at any age; and of course in those rare cases known since 1892 as Dercum's disease (adiposis dolorosa). The appearance of these abnormal fat pads which may become very large and pendulous are well known. They are generally bilateral, although frequently pain or tenderness is confined to one side only. Posteriorly they cover the lower insertion of the inner group of hamstring muscles, being separated by a definite sulcus near the mid-line of the popliteal fossa from the normally present (but probably enlarged) popliteal fat pads described above. Anteriorly they are limited by the internal aspect of the patella, but often appear to blend lower down with the infra-patella fat pad. There is no accompanying sensory abnormality of the overlying skin, although it is often the seat of multiple stellate or spider-like collections of thin superficial veins. Varicose veins and local thrombosis are also a common association as is spontaneous bruising and evening œdema of the ankles. On palpation, distinct lobulation of the contained fat is easily felt, and it can be appreciated that only certain lobules—which feel more tense—are tender. If these be marked it will be found that this localized tense tenderness will affect different lobules on different days. This tenderness appears therefore to depend upon a condition of shifting œdema which moves from lobule to lobule. Excision of the painful fat pad successfully relieves the pain. Microscopical examination shows only œdematous fat of normal structure and with no cellular reaction. These pads are not to be considered as lipomata; the fat is laid down in the reticular areolar tissue between the corium of the skin and the synovial capsule, into the



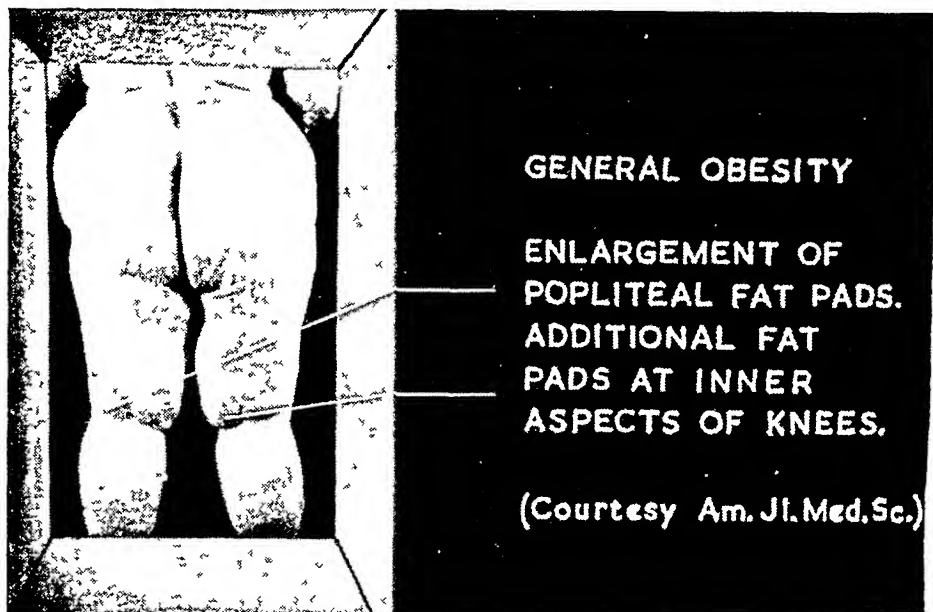


Fig 8

folds of which lobules will often penetrate and adhere. The arrangement of this areolar tissue does not appear to be as a continuous layer but in discrete sheets which when infiltrated with fat lobules in this way have the appearance each of a separate miniature mesentery. The various collections of lobules are thus in fact discrete clumps each with its own blood supply and lymphatic system.

These medial fat pads when they attain a large size can interfere considerably with the free function of the joint, and pain from these is quite frequently referred to the joint itself subjectively; although carefully objective search will reveal a tense peri-articular fat lobule in the pad as its real origin. The differential diagnosis of "arthritis" and its despondent-sounding implications is all too often made in such cases, more particularly if the normally occurring "age-changed" are interpreted as radiological confirmation of this view.

#### ÆTIOLOGY

*Endocrine.*—The cause for the non-inflammatory œdema or water retention which is found locally to be distending the fat lobules which cause pain in the type of fibrositis which has been described, and in panniculitis, is unknown. It may be part of a general condition of dis-function of fat-water metabolism, as it appears to be in those cases which are associated with obesity. It is this factor which accounts for those rapid and otherwise inexplicable variations in weight which occur during the dietetic treatment of the obese. In view of the frequent association of these syndromes with the female menopause (both natural and artificial) it is

tempting to suspect that the underlying cause must be endocrine. It seems to be accepted by endocrinologists that excessive secretion of oestrogens in the human will result in water retention which largely affects the fatty tissues. This is released at a normal period, but if this does not occur the condition may become cumulative. Some reflection of this process is often seen clinically in the cases which have been described. The fault here may lie in the disfunction of the ovarian glands, or more probably further back in the pituitary or hypothalamus. The latter probability is strengthened by the fact that men suffer with these syndromes, more particularly the fibrositic one, quite frequently. Over-activity of the pituitary and the adrenal cortex is known to be associated with pregnancy and the climateric, and commonly results in obesity. In most cases, however, no direct evidence of endocrine disorder is to be found, and it may be surmised that the metabolism regulating centres of the hypothalamus are disordered. This is known to result in water retention, owing to the interference with secretion of the anti-diuretic factor of the posterior pituitary lobe. It is said that in these cases administration of chronic gonadotropin will reduce the subcutaneous fat and release water; and probably the effect of this should be tried in selected cases. It may be presumed that there is no gross pathology present in the majority of the cases which are being discussed, and it seems possible that the lesion may be of genetic determination. The thyroid gland has also been invoked, largely on account of its value in the treatment of certain of these cases; it is thought however that as this substance possesses the property of eliminating excessive tissue fluids, its benefits probably do not reflect any share in aetiology.

Kling, writing (1947) of what he terms Juxta-articular adiposis dolorosa, (probably a condition of panniculitis localised to the joints)—states that no high degree of endocrine disturbance was found in his patients, although B.M.R. estimates were markedly abnormal in a third of them. He also failed to find evidence of interstitial inflammation of sensory nerves but found evidence of increased tissue tension in these sites and considered it probable that the mere increase of the fat tissue causes pressure on the nerve endings and so gives rise to tenderness and pain. Where enlarged knee fat pads were only part of a more generalised condition of adiposis dolorosa, these findings were generally found to be applicable to the other joint areas which were affected.

In spite of the high probability that endocrine imbalance is at fault no generalised abnormality has been detected in the majority of our cases of panniculitis; all routine clinical tests, including the B.P. and E.S.R., were normal. Arthritis did not develop in those cases which were successfully treated for the peri-articular condition. The condition is not necessarily associated with general obesity although it may be; and when it is it tends to be more severe and widespread. Adiposis dolorosa both in its full form and in the peri-articular form described by Kling, may constitute only a variation of this entity.

*Sodium balance.*—Disturbances of water exchange in general betoken dislocation of sodium balance. It can be demonstrated experimentally that cells, including fat cells, swell or contract in a predictable manner in response to variations in sodium concentration in the interstitial fluid; since all cell membranes permit the free passage of water but not of sodium and chloride. The control of water and salt levels is now believed to be controlled largely by activity of the hormone of the posterior lobe of the pituitary, and of the influence of the desoxycorticosterone fraction of the adrenal cortex.

*Genetic factors.*—There may also prove to be a genetic factor involved since close questioning of 50 unselected female cases of severe panniculitis, revealed in nearly half, a history of a similar condition having occurred in the family (mostly in a mother or mother's sister). This is a very high proportion but does not necessarily point to the disease being a familial one since all these patients had been subjected to similar endocrine disturbance as represented by the menopause. It is perhaps more probable that it is the body type which is familial, and panniculitis certainly occurs most frequently in that type which Sheldon (1940) designated as the Endodermic Somatotype.

*Cold.*—It is striking how sudden the first onset of pain may be in some cases, leading occasionally to a wrong diagnosis for this reason alone. It has seemed that in a large number of these cases cold has been the precipitating factor, no doubt merely activating a state already in being. This is understandable in the light of Bazett *et al.* observation (1941) that a temperature gradient exists between the surface of the body and the deep tissues extending inwards to a depth of 2-3.5 cms. and having a temperature difference ranging from 5-15 degrees. The fatty tissues which we believe to be chiefly implicated in the type of fibrositis which has been described, and panniculitis, lie well within this gradient; and since the temperature gradient—and to some extent its depth—vary in response to the cooling power of the atmosphere, these tissues must be directly affected by the external environment. These reactions are no doubt responsible for the well-attested phenomenon of weather-sensitivity in these cases.

### TREATMENT

The pain which occurs in the two main syndromes considered in this lecture, namely, a certain type of fibrositis and panniculitis, has been shown to be due in each case to a painful distension of fat lobules within a confined space. Treatment in both will therefore be along similar lines and have the same objectives. Where these syndromes are complicated by the addition of obesity, the factor of weight reduction will also have to be faced as a primary objective.

The results of treatment at the present time are variable and relapse is common. If the syndrome occurs at the menopause however, as is not uncommon, and remission can be induced for a sufficient period to cover the completion of this process, prognosis is fairly good.

The desiderata of treatment may be epitomized under various headings :

*Diet.*—Since fat is the site of the painful lesion in these cases weight reduction is always indicated even in patients who do not appear to be overweight. It is seldom that any improvement is noted as the result of other methods unless the body weight is falling. Restriction may be limited to starch-containing foods and to fat. Protein foods need not ordinarily be limited.

*Endocrines.*—It has been pointed out that there is clinical evidence that oestrogen tends to cause fluid retention in the tissues, which is released at menstruation, and that in the menopausal patients this condition may become cumulative. Theoretically androgens or progesterone might in such cases be the proper remedy, but very little work has as yet been done on these lines. In menopausal cases the ordinary endocrine treatment should be tried ; in patients who are not menopausal thyroid is nonetheless sometimes helpful, except in those cases who normally show an increased pulse rate. In these cases thyroid extract will generally result in palpitations, but no reduction in weight. There are no known drugs or hormones which will reduce pituitary activity although such an object would seem to be desirable. It is probable that the recent work of Hench, Kendall *et al.* (1949) will be found to be relevant to these syndromes as well as rheumatoid arthritis in due course.

*Diuresis and Dehydration.*—The type of diuresis which is required in these syndromes is that which not only increases the urinary volume, but which also depletes the body fluids—producing thirst. This is the type called by physiologists “obligatory diuresis.” There are several substances which may be employed, and since there is no contra-indication to employing them at the same time it is reasonable to do so.

(a) Chemical substances which act by distorting the internal environment such as urea. This may be given in large doses (e.g., 20 grammes) suspended in a little water or fruit juice after each meal, for long periods.

(b) Chemical substances which alter the acid-base equilibrium and electrolyte balance such as ammonium chloride. This is often given to supplement the action of mercurial diuretics which may also be employed with benefit, and whose effect seems to be to decrease the amount of sodium chloride which is reabsorbed by the renal tubules.

(c) A salt-free diet which is effective in reducing the volume of body fluid where there is an excess. Its effect results from the removal of one of the essential components of this process, whilst restriction of water, the other chief essential, is rendered unnecessary and thirst will thus be relieved.

*Physiotherapy.*—Firm localized massage is used to disperse the swelling where oedematous fat lobules can be felt and are the cause of pain. It will generally prove very painful at first and any reaction caused by this process must be allowed to die down before a subsequent treatment of this sort is administered. In time the patient will become less sensitive, and regular treatment will become possible. Previous exposure to radiant heat and infra-red rays will often increase the patient's tolerance to such

treatment. In cases where actual herniation of fat lobules has occurred—but has not become fixed by adhesions—reduction of the herniation by this method may be possible.

*Injection.*—The object of local injection treatment is to disrupt the swollen fat lobule by hydrostatic pressure, and so relieve the painful tension. Mere infiltration with anæsthetic solution will give temporary relief only, except in those infrequent cases where this procedure has seemed to allow auto-reduction of a hernia, as judged by the subsequent permanent disappearance of both the nodule and the pain. The solution which we have used mostly for this purpose has been novocain 0.5 per cent. in saline. Undercutting or “teazing” with the point of the needle afterwards will complete the disruption. In cases of localized panniculitis the affected area may be thoroughly infiltrated with an oily anæsthetic solution—such as benzyl benzoate—under pressure, with the same object in view. The fibrous compartments separating the fat lobules should afterwards be disrupted with the cutting edge of the wide-bored needle employed, to prevent recurrence.

*Surgery.*—Surgery has no place in fibrositis in which herniation is not a cause. Removal of irreducible fat herniæ which cannot be disrupted by injection, however, remains the logical procedure; and in well-chosen



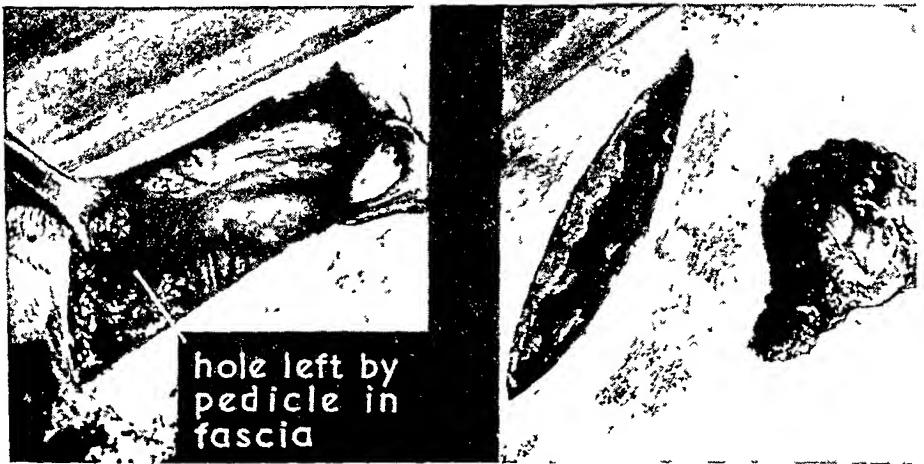
Fig. 9. Operative removal of a fat hernia (J. C. R. Hindenach, F.R.C.S.).  
Stage 1. Hernia seen through superficial fascia



*Stage 2.* Fascia divided Hernia bulging through.

*Stage 3.* Delivery of large fatty Hernia.

Fig. 10.



*Stage 4.* Wound after removal of Hernia.

*Stage 5.* Hernia after removal.

Fig. 11.

cases is highly successful. These structures are sometimes surprisingly difficult to locate in a well-covered person, however, and local anæsthesia is essential as the patient's subjective impressions are often necessary to ensure that it has been rightly localized. The technique of removal is shown in the illustrations, but it must not be forgotten that herniations are sometimes multiple. In cases of panniculitis with obesity, persistent pain which cannot be remedied by other means can sometimes be cured surgically by undercutting the painful area. Presumably the sensory nerves

responsible are cut in the course of this procedure. In two cases of persistent severe pain situated in an enlarged fat pad on the medial aspect of the knee joint, the whole pad was excised with permanent relief of pain to the satisfaction of the sufferers who had found no relief from less drastic procedures.

Several papers have been published in America during the last few years confirming the role played by fat herniæ in the causation of pain in the lumbar and gluteal regions. The largest series is that of Hertz (of Cleveland). In a personal communication (1948) he stated that since 1944 his series of such cases had reached a total of 229 of which he had operated upon 68. At this last follow-up, 62 of these had maintained complete relief from pain. Hutcherson in a paper read before the "Association for surgery of trauma" in July, 1948, reported 42 such cases operated upon, with permanent relief of pain in 40. In England I know of no published series, although I have received accounts of isolated operations of this type which have been followed by success. Amongst surgeons who have communicated with me in this way I wish to thank Messrs. L. E. C. Norbury, S. L. Higgs, Rodney Maingot, Harold Edwards, J. C. R. Hindenach and David Trevor.

### SUMMARY

(1) It is thought that an ætiological classification, although desirable in the case of a "disease entity," must remain impracticable in the case of a syndrome. The classical conception of fibrositis is briefly reviewed and a classification based upon the structure of the nodules found at the source of the pain is tentatively proposed.

(2) Evidence is produced that the fat tissues of the body are subject to pathological variations which cause pain. This pain generally is labelled as "rheumatic" or "fibrositic." When this occurs in the neighbourhood of joints the condition is often wrongly termed arthritic.

(3) It has been shown that several recognisable "rheumatic" syndromes can be the result of an abnormal retention of fluid by fat lobules in certain situations. When this occurs they endeavour to swell, but being confined by indistensible fibrous tissue they are unable to do so, and tension pain results. This œdema shows no sign of being inflammatory in nature.

(4) In some such cases a flaw occurs in the fibrous covering and herniation of the enclosed fat lobule will occur into an adjoining layer. Such herniations may be of three types which are described.

(5) The origin of this selective swelling is probably endocrine. The direct effect of cold may unmask it.

(6) The syndromes described as being due to this abnormality of fat are :—

- (a) "Fibrositis," which occurs in any of the several normally occurring fat pads which are described ; some it is believed for the first time.

- (b) Panniculitis, which occurs in abnormally deposited fat, mostly in predictable sites. Panniculitis may occur with or without general obesity.

In either case the chief sites of pain tend to remain similar. Adiposis dolorosa (Dercum's disease) would appear only to be a quantitative variation of this combination.

(7) Treatment must be directed concurrently along several lines if success is to be achieved. Those discussed include diet, endocrines, diuresis and dehydration, local injections, physiotherapy and surgery.

(8) The indications for surgery are limited, but tend to afford dramatic relief. These are the removal of irreducible fat herniæ, and to a lesser extent removal of localised areas of painful tissue in severe cases of panniculitis.

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The illustrations are from a film-strip kindly made for me by Mr. E. Wilson in the Photographic Department of the Royal Society of Medicine.

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## “OBSERVABLES” AT THE ROYAL COLLEGE OF SURGEONS

### 20. THE PLATE OF THE FACULTY OF DENTAL SURGERY

THE TWO PIECES of plate here illustrated bear the inscription “Presented to the Royal College of Surgeons of England to commemorate the inauguration of the Faculty and Fellowship in Dental Surgery, 31st July, 1947.”

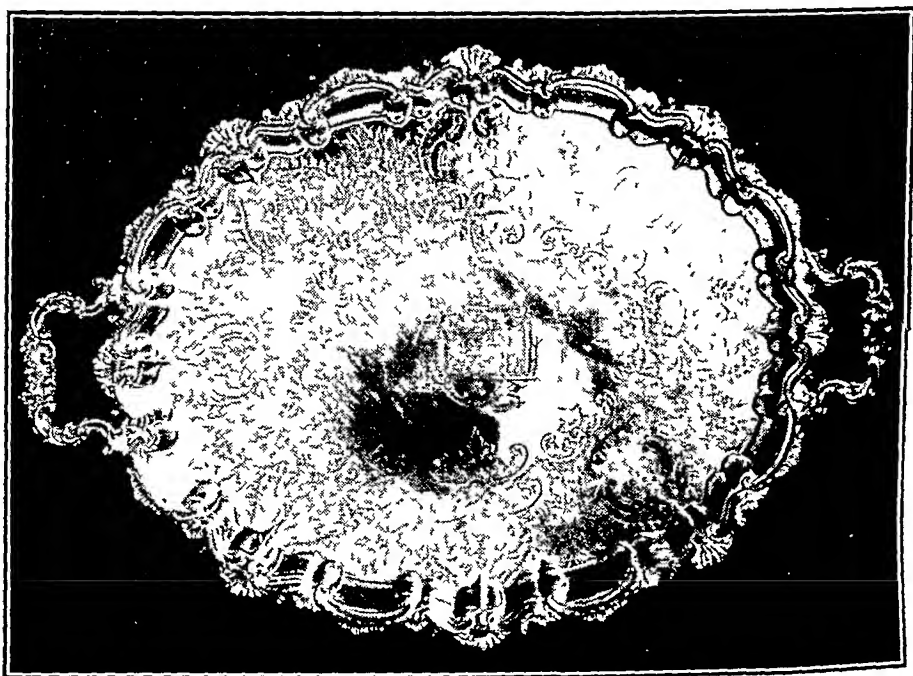
The silver tray was presented to the College by Professor Robert Bradlaw, the first Dean of the Faculty of Dental Surgery. It is of London make in the year 1822-23

The cup, also of silver, was presented by Professor Bradlaw to Sir Alfred Webb-Johnson (as he then was); President of the College, and he in turn gave it to the Faculty of Dental Surgery. It was brought home from India several generations ago by a forebear of Professor Bradlaw, but its earlier history is not known. The design includes several recognizable Indian gods.

The difference in the scale of the two photographs makes it difficult to appreciate the relative size of the objects. The length of the tray is 31 inches and the height of the cup is 11 inches.

These two fine pieces, together with a beautiful silver cupping bowl presented to the College by the late Harry Stobie, were the first of several generous gifts of silver made to the College or Faculty by members of the Board of Faculty.

K.C.





## FOURTH INTERNATIONAL CONGRESS OF OTOLARYNGOLOGY

THE FOURTH INTERNATIONAL Congress of Otolaryngology under the patronage of His Majesty The King was held at King's College, London, from July 18th to July 23rd. The President was Mr. V. E. Negus. Her Royal Highness The Duchess of Kent was graciously pleased to open the Congress.

The first Congress was held in Copenhagen in 1928 and the Congresses of Madrid (1932) and Berlin (1936) followed. The Fourth Congress was the first Congress to be held since the war, and it was attended by over 600 Otolaryngologists from 40 different countries. Many old friendships and contacts were revived, and there was a great meeting of colleagues old and new, which, it is hoped, should have far-reaching and beneficial results. It is a great satisfaction that the organisation built by British Otolaryngologists has been able to bring together so many so long kept apart by the war and its consequences. Scientific Associates were admitted to all scientific meetings and they numbered 123, the majority of them being from the United Kingdom. There were 460 non-scientific Associates registered, many members being accompanied by their families.

There were three main subjects for discussion: "Antibiotics and chemotherapy in the treatment of nasal sinusitis and its complications"; "The treatment of aural vertigo"; and "Non-malignant strictures of the thoracic œsophagus and their treatment." Altogether over 150 papers were read and they covered the whole range of ear, nose and throat surgery. Many members contributed to the subsequent discussions. Thirty-five films of various aspects of the work of the specialty were shown. It is remarkable what great developments have been made in technical improvements in medical cinematography and how the additions of colour and sound have heightened their interest and clarity.

On the afternoons of July 19th and July 21st, groups of members visited the hospitals of London to see operations performed, demonstrations of cases, and methods of treatment and investigation. There were also at King's College interesting pathological, anatomical and historical exhibits as well as displays of surgical instruments, hearing aids and medical books.

During the Congress the opportunity was taken of holding a meeting of endoscopists and thoracic surgeons to revise the nomenclature of the bronchial tree.

The President and Council of the College gave the first St. Clair Thompson dinner on Thursday, July 21st, when their guests were the members of the International Committee and the Executive Committee of the Congress, and the members of the Council of the British Association of Otolaryngologists. The President and Council also held a Reception on the evening of Friday, July 22nd, at which many members of the Congress were received. There was on this occasion a ceremony most pleasing to the foreign guests, and indeed, to ear, nose and throat surgeons all

over the world : Professor F. R. Nager of Zurich was presented by Mr. Negus to receive from the President the honour of the Fellowship of the Royal College of Surgeons of England.

Receptions were also given by His Majesty's Government, by the President of the Royal Society of Medicine and the Presidents of the Sections of Otology and Laryngology, by the President of the British Medical Association and by the Chairman of the London County Council. Over 1,100 were entertained in the gardens of the Zoological Society of London by the President and Mrs. Negus. Many interesting excursions were arranged in and around London during the week for members and their wives. Nearly 1,000 members and associates attended the Congress Banquet held on Tuesday, July 19th, at the Dorchester Hotel. Following the Congress many took advantage of the arrangements made to visit Oxford, Cambridge and Edinburgh, where interesting programmes had been arranged.

The general organisation of the Congress, entailing work for the preceding two years, was largely carried out by the Joint Secretariat of this College. This Secretariat by its efficiency and enthusiasm was of the very greatest help throughout. It was generally agreed by all that the Congress in its many aspects was a great success and Mr. F. C. W. Capps, the General Secretary, deserves congratulations for his magnificent work. The undoubted success of the Congress was largely due to the foresight, knowledge and international reputation of Mr. V. E. Negus ; his associations with his colleagues at home, in the Commonwealth and abroad and his indefatigable work and energy laid the foundation and built, with his British colleagues, the structure of a happy and valuable meeting.

The Fifth International Congress will be held in Amsterdam in 1953.

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### SAYINGS OF THE GREAT

"As is our pathology, so is our practice."—*Osler*.

"The Empire is a Commonwealth of Nations."—*Lord Rosebery*, 1883.

"A lecture should be a cross between an essay and a speech."—*Viscount Samuel*.

"Let your imports be more than your exports, and you'll never go far wrong."—*Dr. Johnson*.

"Scenery is fine but human nature is finer."—*John Keats*.

*Note*.—Contributions are invited.

## FACULTY OF DENTAL SURGERY

### SECOND ANNIVERSARY, JULY 15th, 1949

THE FACULTY OF Dental Surgery of the College, celebrated on Friday, July 15th, 1949, its second anniversary.

In the afternoon the Annual General Meeting was held for the Fellows and Licentiates in Dental Surgery of the College, some 150 of whom were present.

The newly elected President of the College, Sir Cecil Wakeley, K.B.E., C.B., said :

“ Mr. Dean, Members of the Board, and Members of the Faculty of Dental Surgery. It is a very happy coincidence that my first official duty as the newly elected President of this College should be to welcome you here to-day, because I have always taken a close interest in Dental Surgery, and for many years examined for the Licence and latterly for the Fellowship.

“ This is only your Second Annual General Meeting, but when I look through the Second Annual Report of your Board I am amazed at your rapid growth and the variety of your activities. Your Board has worked very hard and especially your Dean, Professor Bradlaw, who by his wisdom and energy has done so much to make the Faculty the success it is.

“ Your profession is passing through a very difficult period, but it has had other difficult periods in its history and overcome them and once again it will, I am sure, emerge triumphant. It would be so easy these days to forget, amongst the spate of conferences, committees, and wranglings, the objects to which we are all dedicated ; service to mankind. Posterity will not judge us by whether we won or lost our verbal battles, but by our devotion to duty.

“ This College has no wish to become involved in political disputes but it has every wish to encourage and promote the art and science of dental surgery and will wholeheartedly support you in this aim.

“ The establishment of the Faculty and the Fellowship in Dental Surgery have been major steps forward in the history of the profession and these, together with the post-graduate activities of the Faculty have already made their mark in this country and have provided even stronger links with our colleagues overseas.

“ Since your meeting last year you will all have heard of the magnificent gift to the College of £250,000 by Viscount Nuffield for the building of a residential college which will enable us to accommodate graduates who are studying surgery and dental surgery. This is a wonderful plan and thanks to the genius of Lord Webb-Johnson, plans are already far advanced to bring about this development. Meanwhile, as an interim measure, we have converted two adjoining houses as residential accommodation for some 20 graduates and I am happy to say that at the present time there are three dental surgeons in residence who are studying for their Fellowship.

"Well, gentlemen, this first Faculty of the College is now firmly established as a very important part of the College and the Council is proud of you. I can assure you that during my term of office I shall regard it as my privilege to do all I can for the Faculty and the profession."

The Dean of the Faculty, Professor R. V. Bradlaw, F.R.C.S., F.D.S.R.C.S.Eng., said :

"Mr. President and Members of the Faculty of Dental Surgery. Last year when I had the privilege of addressing you at our first Annual Meeting, I spoke of the events which led in 1860 to what may be regarded as the foundations of dental surgery in this country.

"To-day I wish to speak of the future. I cannot do better than to begin by reminding you of the words of Lord Webb-Johnson when we last met :

'Your aims are to advance the science and art of dental surgery. Your objectives to improve dental education and to advance research, to set standards of competence and to establish higher standards for those aspiring to leading positions as teachers, consultants and investigators.'

"These are difficult times when abuses are publicised but honest endeavours rate no headlines. But we have met difficulties before this and have surmounted them. Those who went before us travelled no easy road. Misunderstandings and controversies beset them and there were many heart-burnings before the way was clear. Let us accept the challenge which the future affords us and make the best of the opportunity we have to advance the science and art of dental surgery by every means open to us.

"How may the Faculty help ? By tradition the College has no political aims but yet there are many ways in which it has furthered those ideals of service to the community and advancement of the healing art, to which this Faculty is pledged. Already our sister College of Edinburgh has instituted a Fellowship in Dental Surgery and courses of advanced study. To these, as to our own, will come men and women who will take away with them throughout the country and to the four corners of the world, not only the skill and knowledge which they have gained and of which they have given proof, but something intangible, the tradition of Hunter, Tomes, Hebburn and all those who laboured for that which we have inherited.

"Here in library and laboratory, in lecture theatre and museum are the tools of learning. But more than this they will find here those who are eager to help them and to give freely of the experience which only the years can bring, and if they are privileged to be in residence either now or in the College of Surgical Science which Lord Nuffield's munificence has made possible, they will have opportunities which an older generation can but envy.

"We hope, too, to afford wider opportunities for research and to encourage original work in dental science. The John Tomes Prize and

the Cartwright Prize and Medal, recognise achievement in this field. The Charles Tomes Lectureship enables the College to honour those who have made contributions to knowledge; it has now been decided that Fellows in Dental Surgery shall be eligible for the Arris and Gale Lectureships which were founded in the 17th Century.

"We seek to create a wider fellowship than that attainable by examination or election, a fellowship of high purpose and endeavour. I believe that we shall succeed.

"It is my happy duty to inform this Annual Meeting to-day that your Board has resolved to institute a lectureship to be known as the Webb-Johnson Lectureship which will commemorate for all time the indebtedness of our profession to Lord Webb-Johnson.

"Mr. President, we wish to thank you and the Council for your encouragement and help during the past year. Our profession will be ever mindful of its indebtedness to the College for all that it has done. It has the affection and loyalty of its Fellows and Licentiates in Dental Surgery throughout the Empire and many lands. Of that you have material evidence in the gifts which have been received especially in the beautiful and historic silver which Professor Sprawson has presented to us and in the Commemoration Fund to which more than £2,500 has been generously subscribed. It is our desire to be worthy of the great traditions of this ancient College.

"I wish to thank my colleagues of the Board of Faculty for their support during the past year and to express my appreciation of the work of the Chairmen of Committees, the Vice-Dean, Professor Wilkinson, Mr. Fish, Mr. Kelsey Fry and Mr. Senior. Especially do I thank Mr. Davis, the Secretary of the Faculty.

"We are deeply grateful to him."

The Annual Report for the year was presented by Mr. E. W. Fish. The Report will be circulated in due course.

It was reported that at the elections held on the morning of July 15th Mr. Kelsey Fry, Professor Wilkinson and Mr. Shefford had been re-elected to the Board of Faculty by the Fellows of the Faculty.

Mr. Bryan St. J. Steadman and Mr. K. E. Pringle were elected to the Board to represent the Licentiates in Dental Surgery of the College.

At the end of the Annual General Meeting an impressive ceremony took place during which the following were presented by the Dean of the Faculty to the President of the College for admission to the Fellowship in Dental Surgery :

PROFESSOR E. LAPIRA :—*President of the Maltese Dental Association.*

DR. H. W. REID :—*President of the Royal College of Dental Surgeons of Ontario.*

DR. C. W. FREEMAN :—*Dean of the Dental School, North-Western University; President Elect of the American Dental Schools.*

DR. K. THOMA :—*President of the American Academy of Oral Pathology.*



The President, Sir Cecil Wakeley, conferring the Honorary Fellowship in Dental Surgery on Professor Kurt Thoma.



DR. F. M. WATRY :—*Secretary-General F.D.I. Technical Counsellor to Belgian Ministry of Social Security.*

LT.-COL. J. L. BERNIER :—*Chief of the Division of Dental Pathology, United States Army.*

Immediately after these ceremonies, a large and distinguished audience had the pleasure of hearing Professor Kurt Thoma deliver the first part of the Charles Tomes Lecture on "Odontogenic Tumours of the Jaws."

In the evening a Dinner was held at the College, and among those present were :

Lord Webb-Johnson, Sir Wilson Jameson, Miss Russell Smith, Mr. Farrer-Brown, Maj.-Gen. Bullen Smith, Dr. M. Suttill, Mr. J. Baird, M.P., Professor Kurt Thoma, Professor F. M. Watry, Dr. F. M. Watry, Lt.-Col. J. L. Bernier, Professor C. W. Freeman, Dr. Ghosh, and Brig.-Gen. Ehsan.

The toast of the College was proposed by the Dean, and replied to by Sir Cecil Wakeley, K.B.E., C.B., President of the College.

The health of the Guests was proposed by Mr. E. W. Fish, and replied to by Mr. L. Farrer-Brown, J.P., and Dr. W. Harvey Reid.

In addition to these toasts, the health of the Past-President, Lord Webb-Johnson, K.C.V.O., C.B.E., D.S.O., T.D., was proposed by Dr. Senior. Dr. Senior stressed all that Lord Webb-Johnson had done for the College and for Dental Surgery and the high regard in which he was held by everybody.

The toast of the health of Lord Webb-Johnson was then proposed with tremendous acclamation.

The Dean presented to Lord Webb-Johnson a small gold snuff-box as a token of the regard and affection of the Board.

Lord Webb-Johnson replied in his own inimitable style and outlined his views on the past and future of the College.



The Dinner of The Faculty of Dental Surgery

THE LIBRARY  
TWO NEW LETTERS OF EDWARD JENNER

ON THE OCCASION of Edward Jenner's two hundredth birthday anniversary Dr. Mervyn Gordon F.R.S. has generously presented the College with two autographs of Jenner, each of which is of interest for the light it throws on a particular aspect of his work.

The earlier letter comes from a collection of autographs formed by William Buckland, Professor of Geology at Oxford, and later Dean of Westminster and a Trustee of the Hunterian Museum. It is addressed to Mrs. Benjamin Morland, who was the step-mother of Buckland's wife. Both Professor and Mrs. Buckland were famous for their versatile and sometimes eccentric interest in every aspect of scientific enquiry, a tradition carried on by their son Frank Buckland, who was the prime mover in organizing the reburial of John Hunter in Westminster Abbey in 1859, and himself made the long search to recover Hunter's coffin in the vaults of St. Martin's.

After the first enthusiasm at the discovery of vaccination in 1798, various difficulties were encountered in its practice. There was much latent prejudice against vaccination, and Jenner's opponents took full advantage of every apparent failure in order to discredit his work. Jenner fervently believed in the necessity for the public welfare of spreading a right knowledge of his methods, and was consequently at pains to explain the cause of every failure from his own wide experience and prolonged consideration of the subject. He published articles and pamphlets and took infinite trouble in writing private letters, to counteract what he believed to be dangerous to public and private health in the opposition to his work. This letter is typical of his method of allaying the fears and hesitations of a parent alarmed by reports that vaccination was not a sure preventive of small-pox.

LETTER OF 4 MARCH 1804.

Berkeley Glo/re.

MADAM,

March 4th, 1804.

Having some time since heard that a report was current in Town that a child of a Mr. Grant at Portsmouth had received the smallpox after it had been inoculated *by me* for the cowpox, I requested a friend in Town (Mr. Ring, Surgeon in New St., Hanover Square) to make an inquiry into the business. Mr. Ring immediately wrote to Mr. Grant, who explained the matter in a very candid and satisfactory manner. It turned out to be nothing more than one of those rashes which an irritable skin is very apt to push out on the application of acrid substances, particularly the animal poisons. Seeing that such cases must necessarily occur I did not omit to guard the World against false alarms in my earliest publications on the vaccine subject: but unfortunately without a knowledge of the Vaccine Disease, or the smallpox; entirely ignorant too of the laws of the animal œconomy, prejudiced persons like Mr. Seaton, dash into the subject, reason and decide at once. One would suppose from reading this gentleman's letter that vaccination was a project of a month old. Could anyone imagine that at the time Mr. S. penned it millions of persons having

been inoculated for the cowpox, had been exposed to the infection of the smallpox without feeling any ill consequence? Had the child of Mr. Grant been exposed to the effluvia of smallpox no ill consequence would have ensued. In a word, the experience of the world (for all civilised nations have now adopted vaccine inoculation) allows me to say that no one who has passed through the vaccine disease correctly, ever caught the smallpox after the most rigid exposure to it, even in its most active and malignant forms.

I have the Honour to be Madam,  
your very faithful humble servt.

E. JENNER.

P.S. If I recollect right I had an interview with Mr. Morland at Benson in my way from Town on the subject of the Inoculation of your Infant.

The second letter was written near the end of Jenner's life when he was much occupied with the practice of counter-irritation by means of antimonial ointment, which he considered a remedy for a wide variety of disorders. His observations had been made intermittently through fifty years, for his earliest writing was on the production of preparations of antimony. During 1819-21 he was prescribing this treatment assiduously and compiled a record of his results in the autumn of 1821, which was published next spring as "A letter to Charles Henry Parry, M.D., F.R.S. on the influence of artificial eruptions, in certain diseases of the human body."

LETTER OF 30 DECEMBER 1821.

To Farmer Paradise,  
Wick.

DEAR FARMER,

The account you have sent me in your letter by Farmer Dimeny is very clear and explicit. I wish for your sake that it had been a pleasanter one.

As the blisters seem to afford some relief I would wish you to persist in their use by applying a fresh one on a sound part of the skin when the discharge ceases. In cases like yours I have often known cream of tartar produce excellent effects. When you can find out the proper dose, it will act mildly on the bowels; and you may take it every morning in the quantity of two teaspoonfuls in a small tumbler of water. About a tablespoonful of boiling water will take off the chill. The cream of tartar will not dissolve, but must be well stirred up when you take it.

This is all we will do at present unless you think well of taking the mixture in the way you mention. When taken at night it will not interfere with the opening effects of the cream of tartar. I would wish you also to use the ointment to help out the eruption.

Pray let me hear again in a few days, and  
believe me  
very sincerely yours

Berkeley, 30 Decr. 1821.

EDW. JENNER.

You may increase or lessen the dose of cream of tartar according to its effects. It is intended to act mildly on the bowels.

The first letter was printed in *Brit. Med. J.* 1937, 2, 675; the second has not been published before.

## MONTHLY DINNERS

Monthly dinners are held in the College on the Wednesday before the second Thursday of each month. The following are entitled to attend with their guests : All Diplomates and students of the College and Members of the Associations linked to the College through the Joint Secretariat. It is not necessarily intended that guests should be members of the medical profession.

The dinners will be at 7 p.m. on the following Wednesdays : October 12, November 9, and December 7, 1949, January '11, February 8, March 8, April 12, May 10 and June 7, 1950. There is an inclusive charge of £1 5s. (including drinks), which must be sent with the application to the Assistant Secretary at least a week before the date of the dinner. The dress is Lounge Suit or Uniform.

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There will be no lectures at the College during August, but the Museums and Library are remaining open.

## DIARY FOR SEPTEMBER

Thur. 1	5.00	Otolaryngology Lecture.
Thur. 8		Pre-Medical Examination and Second L.D.S. Examination begin.
Thur. 15		First Membership Examination begins.
Fri. 16		D.C.H. Examination begins.
Wed. 21	11.00	MR. R. J. LAST—Urology Demonstration.
Fri. 23	11.00	MR. R. J. LAST—Urology Demonstration.
Tues. 27		Final Membership Examination begins.

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## THE RESTORATION AND DEVELOPMENT FUND

Recent contributions to the Restoration and Development Fund include one hundred guineas from Mr. Brian W. Windeyer of The Middlesex Hospital. The total is now almost £196,000.

# OSTEOGENIC TUMOURS OF THE JAWS

Charles Tomes Lecture delivered at the Royal College of Surgeons of England  
on  
15th July, 1949  
by

Kurt H. Thoma, D.M.D., F.D.S.R.C.S.

Professor of Oral Surgery, Emeritus ; Charles A. Brackett, Professor of Oral Pathology,  
Harvard University

THESE TUMOURS ARE MADE up of tissue derived from osteogenic mesenchymal cells, which when fully differentiated are osteoblasts. So here again we may encounter benign and malignant neoplasms made up of cells, the development of which may have been arrested at various stages of their growth. Osteogenic tumours, therefore, may be made up of simple spindle cells, chondroblasts and osteoblasts. These tumours do not necessarily produce bone ; they may form myxomatous tissue, collagen, osteoid, or cartilage. In the benign osteogenic tumours, all cells, as a rule, reach the same stage of differentiation ; while in malignancy, because of rapid growth, two or more types of tissue may be seen simultaneously or at different periods of their existence.

On this basis, the following classification may be made :

## Osteogenic Tumours

Osteoma :	Fibrosarcoma :
osteoma durum	peripheral
osteoma spongiosum	central
Chondroma :	Fibro-osteoma :
peripheral	ossifying fibroma
central	osteoid osteoma
Osteogenic myxoma	mature osteoma
Osteogenic fibroma :	Osteogenic sarcoma :
peripheral	osteolytic
central	osteoblastic

## OSTEOMA

This is a benign tumour, which generally occurs as an expansive formation growing from the periphery of the cortex of the jaw to which it is attached. The attachment may be in the form of a flat pedicle or occur over a wide base. Osteomata generally develop slowly and produce a gradually increasing tumefaction in the oral cavity or deformity of the face. We distinguish microscopically the osteoma durum with an eburnated, lobulated surface, made up completely of dense cortical bone and scant fibrous stroma, and the osteoma spongiosum in which cancellous bone predominates. The marrow substance in these is replaced by dense fibrous tissue.

Osteoma of the mandibular condyle has been reported, though it is classified by many (Rushton, 1944)<sup>1</sup> as a hyperplasia. A lobulated,

spherical unilateral enlargement of the condyle causes occlusal abnormalities, oblique attrition of the teeth, facial asymmetry (Fig. 12A), and dysfunction of the mandibular joint with limitation of motion. I have seen two such cases; in each the histological examination showed normal bony structure with red marrow in the marrow spaces. Roentgen examination should be made from a postero-anterior projection as this gives the clearest picture of the enlargement that has occurred (Fig. 12B).

Osteomata are found also in multiple form. Fennel (1938)<sup>2</sup> described the case of a patient who had so many osteomata throughout his entire skeleton that he was colloquially known as "Knobby Willy." I took care of a patient who had numerous osteomata, principally in the facial skeleton (Thoma, 1936)<sup>3</sup>; multiple at each side of the inferior border of the mandible, two at the right ascending ramus, one in the right maxillary sinus (Fig. 13), one attached to the mastoid process, and a small one forming in the apex of the orbit.

### CHONDROMA

Although it is generally assumed that chondroma in membranous bones forms from cell rests of the embryonic cartilaginous skeleton, it is true that it may also form by differentiation of mesenchymal cells into chondroblasts. The tumour is extremely rare in benign form, though cartilage is frequently seen in osteogenic sarcoma. It consists of irregularly arranged, vacuolated cartilage cells producing hyalin intercellular substance, and sometimes osteoblasts which give rise to osteoid or bone.

Chondroma may form as a central tumour or as an outgrowth from the surface of the bone. A globular tumour of the latter type which was attached to the alveolar process in an edentulous area was reported by Dr. Francis McCarthy\*. A maxillary chondroma causing great deformity of the face in a patient 52 years old was seen by Dr. C. C. Simmons†, and Dr. M. Jacobs (1942)<sup>4</sup> published a case of a chondroma of the mandible, which, however, may be classified as a fibro-osteoma (Fig. 18F).

### MYXOMA

Myxoma and fibromyxoma are, as we have seen, generally of odontogenic origin. Differentiation is not easy, however, and there is a question in my mind whether cases of osteogenic myxoma can always be distinguished by either microscopic or roentgenologic investigation. As a clinical criterion, one may use the rather malignant behaviour of the osteogenic type, which resembles that encountered in other parts of the skeleton. The odontogenic type, as has been pointed out in the previous paper, being benign, recurs seldom if carefully enucleated. The osteogenic type I have encountered in a case confined to the mandibular condyle, far enough away from the region where odontogenic activity

\* THOMA, K. H. (1949) *Oral and Dental Diagnosis*, 3rd edition, Philadelphia, W. B. Saunders Co., p. 448.

† THOMA, K. H. (1934) *Clinical Pathology of the Jaws*, Springfield, Ill., Charles C. Thomas, p. 457.



A



B

Fig. 12. Osteoma of Mandibular Condyle. A.—facial deformity ; B.—Roentgenogram.





Fig. 13. Multiple Osteomata of Mandible and Maxilla.

occurs to classify it as an osteogenic myxoma (Fig. 14). Resection of the condyle in the healthy bone of the ramus completely cured the patient.

### OSTEOGENIC FIBROMA

The osteogenic fibroma may occur as a peripheral and as a central tumour. It is made up of fibroblasts which deposit collagen fibres. These constitute the main part of the avascular tumour in which a few spicules of bone may form.

### PERIPHERAL FIBROMA

Peripheral fibroma arises from the periosteum of the jaw and is generally situated on the alveolar process, where it is known as epulis fibromatosa. This tumour is well known and of frequent occurrence.

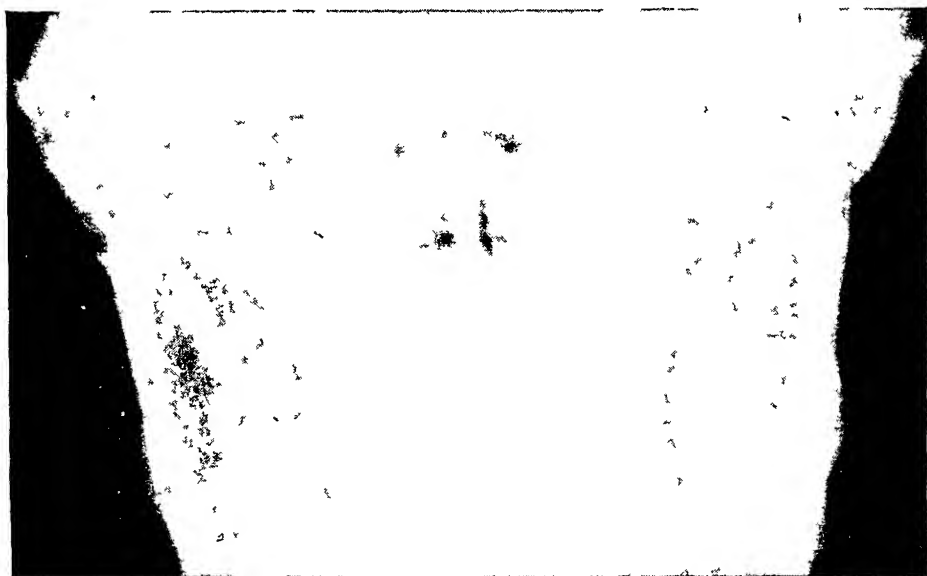


Fig 14. Myxoma of Mandibular Condyle.

### CENTRAL FIBROMA

Intraosseous fibromata are uncommon. They are said to arise in the maxilla from the periosteum of the maxillary sinus, causing a gradual enlargement of its walls by pressure. I have not seen this type. They may form in the mandible from the connective tissue of the perineural sheath of the inferior alveolar nerve (neurofibroma), but mostly they are formed from the dental follicle. These have already been described under odontogenic tumours. A central fibroma appears in the X-ray as a well-circumscribed cystic area. Because of a tendency to form osseous structures this tumour generally develops into an ossifying fibroma or fibro-osteoma, which will be described later.

### FIBROSARCOMA

Again we encounter peripheral and central tumours. Those which occur on the oral aspect of the jaws tend to be less malignant than those which arise from the region covered by skin.

*Peripheral fibrosarcoma* varies in rapidity of growth as well as in malignancy. In the mouth, they form bulky nodular tumours (Fig. 15), sessile in character, bluish red in colour, often presenting an ulcerated surface when injured by the teeth in the opposite jaw. At the cutaneous part of the jaw, the tumour forms from the periosteum and generally grows expansively and with great rapidity. It soon invades and destroys the bone. It occurs at the angle of the jaw, the symphysis, and once in my experience, it arose from the condylar part of the mandible causing a swelling under the skin in the preauricular area.



Fig. 15. Peripheral Fibrosarcoma of Mandible.

The tumour may be easily diagnosed from the roentgen picture, as the tissue is quite dense and frequently shows invasion and destruction of bone.

It is likely to recur even after radical removal, and visceral metastases occur early through hematogenous transportation of tumour cells.

*Central Fibrosarcoma.* The central variety may arise from the connective tissue of the nerve trunks or blood vessels. This tumour may not be recognized when small unless routine X-ray examination discloses it. It appears as an osteolytic area. It is infiltrating in character and may break through the bone. Symptoms occur when the teeth are encroached upon. They become loose and are often extracted without the disease being recognized. Pain and swelling of the expanding jaw are other signs. The maxillary sinus and the nasal cavity may be involved, and the orbit may be encroached upon, causing exophthalmos. Pathological fracture may occur in the mandible (Fig. 16). The histological make-up of fibrosarcoma may show spindle-shaped nuclei, oval cells with vesicular nuclei, or large cells with pleomorphic nuclei, together with tumour giant cells. The number of mitotic figures varies with the rapidity of growth (Fig. 17).



Fig. 16. Central Fibrosarcoma with pathological fracture of mandible.

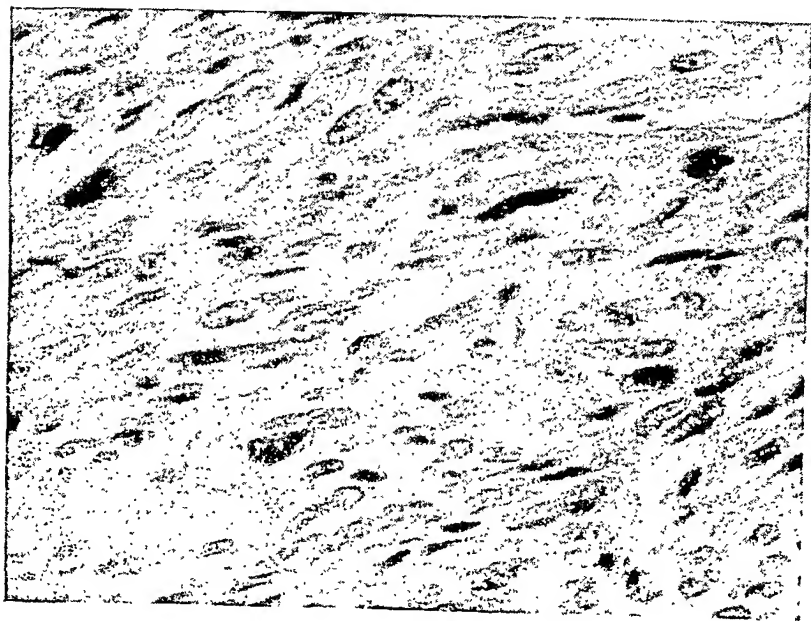


Fig. 17. Photomicrograph of section from Fibrosarcoma shown in Fig. 16.

## FIBRO-OSTEOMA

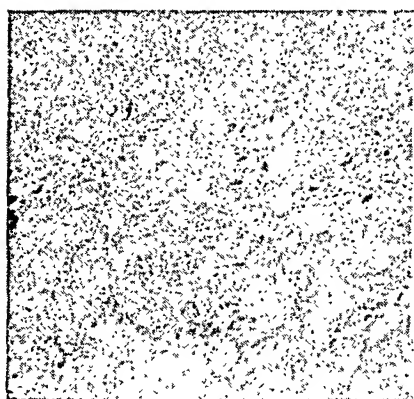
This is a benign tumour which originates in the marrow spaces of the spongiosa. The tumour, because of its great variability in the proportion of fibrous to osseous tissues and the varying degrees of calcification encountered, has been described under many different names, i.e., ossifying fibroma, osteofibroma, fibrous osteoma, by those who concede that it is a tumour, while others who dispute its neoplastic nature prefer the terms localized osteitis fibrosa, localized osteodystrophia, and monostotic fibrous dysplasia. Schlumberger (1946)<sup>5</sup> of the Army Institute of Pathology in Washington, who reported 67 cases of fibrous dysplasia, including five of the maxilla and two of the mandible, feels that the disease represents a non-specific abnormal reaction to injury, producing a connective tissue overgrowth. He points out that similar connective tissue replacement of the marrow cavities and cancellous bone is seen in osteomyelitis, osteomalacia, rickets, and the healing of fractures, as well as in certain systemic diseases such as generalized osteitis fibrosa, and osteitis deformans. The fibro-osteoma, however, has no constant relationship to injury and does not represent, according to my findings, a reparative process of a variety of local or systemic factors. It develops without apparent cause and cannot be associated with regional injury or infection. Nor are vitamin deficiencies or endocrine influences, such as hyperparathyroidism, associated with it, since in none of the cases could an abnormal blood chemistry be discovered. Also, no relationship with neuro-fibromatosis has been established, since none of the facial cases in my experience presented areas of pigmentation, so-called "café au lait" spots, described by Albright, Butler, Hampton and Smith (1937)<sup>6</sup> and lately by Tannhauser (1944)<sup>7</sup>.

From my clinical findings and pathological study, I can only deduct that the fibro-osteoma is a tumour which causes the marrow spaces to be filled with actively proliferating young osteogenic connective tissue cells. As the tumour tissue accumulates, resorption of the bone trabeculae takes place, and later when more tissue is formed, the region of the jaw in which the tumour formed, expands. This process is similar to the development of a tumour formed from hemopoietic tissue, such as a myeloma, except that in the fibro-osteoma the tumour cells also produce intercellular substance which is not the case in myeloma.

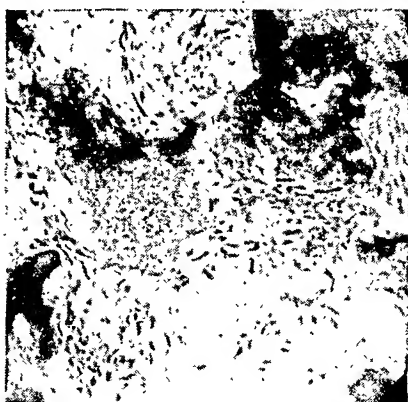
The formation by metaplasia of various types of new but abnormal bone is a characteristic of the degree of differentiation and versatility of the osteogenic tumour cells. For this reason various types of fibro-osteomas may be observed.

In some cases the fibrous tissue predominates and grows massively, replacing completely the trabeculae of the old spongiosa. New immature bone trabeculae may be laid down in certain places (Fig. 18A). This type we may conceivably call ossifying fibroma if a subdivision is desirable.

# OSTEOGENIC TUMOURS OF THE JAWS



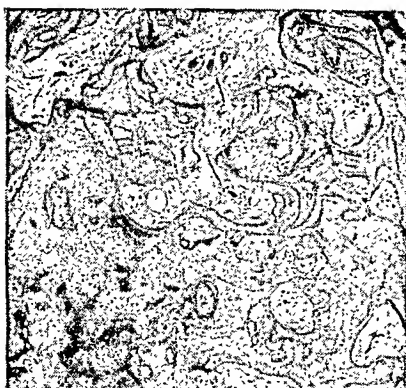
A



B



C



D



E



F

Fig. 18. Fibro-osteoma :—Photomicrographs of: A.—ossifying fibroma; B.—intercellular deposit of osteoid; C.—trabeculae of osteoid; D.—mature bone trabeculae with cement lines forming mosaic pattern; E.—focus of giant cells causing bone resorption; F.—fibro-osteoma with formation of cartilage.

In the second type, the osteogenic connective tissue cells fill the marrow spaces of the spongiosa, forming immature, so-called fibrillar bone from condensed, hyalinized, intercellular substance, which is deposited around them (Fig. 18b), while the trabeculae of old bone are undergoing osteoclastic resorption. In other instances, the bone is partly or completely replaced by trabeculae of osteoid and, in some cases, lamellar bone (Fig. 18c). The immature fibrillar bone is formed by fibroblasts of a low level, while the trabeculae are produced by fibroblasts of a higher level of differentiation. The newly formed bone has irregularly placed osteophytes, and there is evidence of apposition and resorption. The osteoid in these tumours is so typical that the term fibro-osteoid osteoma seems fully justified.

A third mature type may be distinguished. In this, new bone trabeculae have become completely calcified, and the marrow has become acellular or fibrous in nature. The trabeculae again are arranged irregularly and show evidence that resorption and apposition had been actively going on previously. They are united by broad cement lines, which stain deep blue and provide a mosaic pattern (Fig. 18d).

The main characteristic of the fibro-osteoma, therefore, is the formation of atypical bone by direct metaplasia of connective tissue. The cells are rounded out, present vesicular nuclei and are surrounded by profuse deposits of osteoid which calcifies slowly but not completely and stains deeply with eosin. In other cases, the cells have applied themselves to the periphery of metaplastic bone, forming more or less calcified atypical bone trabeculae. In most cases osteoblasts are numerous, and in some cases areas rich in giant cells may be noted (Fig. 18e). The histological appearance often varies in an individual lesion and areas of myxomatous tissue and cartilage have been found in the cases reported by Phemister (1937)<sup>8</sup>. The case of Dr. Jacobs (1942)<sup>4</sup>, referred to as *chondroma*, may fit into this classification, since the greater part of the tissue had the character of a fibro-osteoma (Fig. 18f).

The clinical features of fibro-osteoma are quite as characteristic as the pathological make-up of the tumour. The tumour occurs in the maxilla as well as the mandible. Bilateral involvement and simultaneous maxillary and mandibular occurrence (Fig. 23), has been observed by Phemister and Grimson (1937)<sup>8</sup> and Thoma (1949)<sup>9</sup>. In this respect, therefore, fibro-osteoma resembles the peripheral osteoma, which also occurs in multiple form.

The tumour has a predilection for individuals in the second and third decades of life. The early stage of the tumour is rarely seen because of the absence of symptoms. It is generally discovered when the expansive growth produces facial deformity, which may be considerable, or disturbances in the occlusion of the teeth. The duration of the tumour is, therefore, difficult to ascertain; patients state it to be from one to 30 years. No cases have been reported that have undergone sarcomatous changes.



Fig. 19. Fibro-osteoma of maxilla involving maxillary sinus and malar bone.  
(Photomicrograph shown in Fig. 18c.)



Fig. 20. Fibro-osteoma of mandible with expansion of bone.





Fig. 21. Fibro-osteoma of mandible, osteoporotic type. (Photomicrograph shown in Fig. 18E.)

In the maxilla the typical case includes obliteration of the maxillary sinus and causes expansion of the canine fossa as well as the palate. The malar bone is generally involved and the eye may be pushed to a higher level causing diplopia. Curiously, the nasal wall is not involved, and the nasal passages remain normal. The roentgen film shows a characteristic picture, a dense mass is seen filling the maxillary sinus and obliterating its walls (Fig. 19). In a side view, the increased density gives a shadow of a typical stippling, particularly if the tuberosity is involved and enlarged. This effect, as Worth (1937)<sup>10</sup> pointed out in an article in the *British Journal of Radiology*, resembles the texture of orange peel.

The radiopacity of the tumour, of course, depends on the amount of osteoid and degree of calcification present.

In the mandible, the lesion may be limited in extent or may involve a large part of the bone, causing expansion of the alveolar process with irregular deformity of the chin or side of the face. Roentgen examination may reveal a circumscribed area of decreased density, which may be cystic in character, or it may show diffuse involvement without distinct demarcation. In some cases the cortex is expanded with convex bulging and thinning of the inferior border of the jaw (Fig. 20). A case of this type, which I would classify as fibro-osteoma, was reported by Rushton (1946)<sup>11</sup>. The radiopacity of the bone varies greatly. In the type for which the term ossifying fibroma has been suggested, the tumour is mostly radiolucent, though there may be islands of greater density due to deposit



Fig. 22. Fibro-osteoma of mandible, hyperostotic (mature) type in woman 56 years old, involving both maxillæ and mandible. (Photomicrograph shown in Fig. 18D.)



Fig. 23. Fibro-osteoma of mandible-hyperostotic type.

of partly calcified osteoid. Extensive but gradual resorption of the calcified bone trabeculae and cortex also causes a radiolucent defect (Fig. 21), while the replacement by ossifying fibrous tissue gives an irregular granular appearance. If mature bone is formed, circular or jagged areas of great density result (Fig. 22). The hyperstotic form of the tumour seen in older individuals presents a very radiopaque appearance and gives the picture of an osteoma (Fig. 23).

### OSTEOGENIC SARCOMA

The registry of Bone Sarcoma of the American Collège of Surgeons includes under this name all malignant tumours derived from ancestors of cells, which, when duly differentiated are known as osteoblasts.

Because of the rapidity of growth, we may see all stages of development of the osteogenic mesenchymal cells with production of their respective intercellular substances, fibroblasts, with collagen and myxomatous tissue, chondroblasts and cartilage, and osteoblasts depositing osteoid or bone.

Jaffe (1935)<sup>12</sup> suggested that osteogenic sarcoma may be the malignant counterpart of osteoid-osteoma and indeed there is much that could be said in favour of linking fibro-osteoma with osteogenic sarcoma, except that it would suggest unnecessarily and needlessly a bad connotation on a benign and harmless disease.

Clinically, we find that the osteogenic sarcoma occurs most frequently in young, strong and vigorous individuals and has an extremely poor prognosis. It may involve the maxilla or the mandible, causing pain, a sense of pressure with loosening of the teeth, and paresthesia of the face.

Osteolytic and osteoblastic types are generally recognized, though both conditions may be presented in one tumour. In those predominantly osteolytic, a great deal of bone is destroyed and replaced by fibrous and myxomatous tissue and cartilage, while in the osteoblastic or sclerotic variety, there is a high degree of bone produced, not only in the tumour but also subperiosteally. The latter causes the well-known "sunray" effect. In other cases, osteolytic and osteoblastic formation may be balanced in such a manner that very little change in radiability can be demonstrated.

The roentgen examination is important and gives a great deal of information regarding the part of the jaw involved. Signs which are diagnostic were set down by Codman (1926)<sup>13</sup>. These are combined central and subperiosteal involvement, the presence of the old shaft or cortex in the tumour, the invasive character of the tumour, osteolytic and osteoblastic components being present simultaneously, and involvement of the soft parts which surround the bone.

The clinical course and rapidity of growth vary greatly. Osteoblastic tumours usually grow slowly and are not very malignant, while the soft vascular type which shows cells of great variation in size and shape with many mitotic figures, has a very poor prognosis. Recurrence after even very radical surgery is not uncommon and metastases form in the lungs rather than in the lymph nodes and bones. Most cases end fatally inside of two years.

## TREATMENT OF OSTEOGENIC TUMOURS

Most of the benign, highly differentiated osteogenic tumours are treated simply by excision. The mandibular condyle if involved, generally must be resected. The fibro-osteoma presents a greater problem. Only in very small early lesions can the tumour be completely excised. In most cases the jaw is so extensively affected that the operation should be limited to partial removal to eliminate a deformity, keeping in mind that slow recurrence calls for over- rather than for under-correction. I noted that in a report by Dr. Martin Rushton, published in the *Proceedings of the Royal Society of Medicine* (1947)<sup>14</sup>, a patient was treated by radiotherapy preparatory to a cosmetic reduction of the bony prominences. The procedures we have experimented with are the reverse; we have followed Phemister and Grimson's advice to treat the patient with irradiation postoperatively. We have administered to three patients 150 R. twice a month for six months, but found that it did not greatly alter the course of the tumour. Phemister and Grimson, however, recommend a total of 3,000 R. given in a similar way over a protracted period of time. In many cases repeated cosmetic surgical procedures are required and with advancing age, no doubt, the tumour attains a state of maturation of the bone with atrophy of the cellular elements, eliminating further growth.

The malignant tumours, especially the osteogenic sarcoma, require prompt radical interference, not only of the affected bone, but of the surrounding tissues as well. Radical resection may occasionally save the life of the patient, although the prognosis is invariably very poor.

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# RECOLLECTIONS OF LORD LISTER

by

L. V. Cargill, F.R.C.S.

HAVING BEEN INVITED to write a short contribution for the *Annals* on my period of service with Lord Lister and being one of the last to win his Clinical Surgery Prize and perhaps the last surviving House Surgeon, I feel that it is a duty to do my best by adding just a few personal notes to the numerous testimonies and reminiscences which so many eminent contemporary workers and old pupils have already given to the world.

In spite of an interval of 58 years since I was House Surgeon to Sir Joseph Lister, Bart., as he then was, I still remember many of the events which impressed me.

From King's College School, which was at that time in the Strand, I passed into King's College to prepare for a Science degree. Learning from students of King's College Hospital, then in Portugal Street (just behind the Royal College of Surgeons), of the great surgeon there, who had revolutionised Surgery, I decided to enter the Medical Department and endeavour to train under him.

Whilst engaged on the preliminary studies in Anatomy, Physiology and Chemistry at King's College, I had learnt that Lister's marvellous achievements in dealing with wounds had been inspired by Pasteur's discoveries that fermentation and putrefaction were caused by the presence and growth of minute living organisms.

In pre-anæsthetic days rapidity had been the chief qualification of an Operator, but with the introduction of Anæsthetics, the excellence and permanance of results became the great aim. This was promoted by Lister's introduction of antiseptics which with scrupulous cleanliness, eliminated infection with the microbes causing suppuration, erysipelas, septicæmia and gangrene, and ensured asepsis and perfect healing, thus extending the scope of Surgery beyond measure, robbing the operating room of its terrors and convalescence of its perils.

Lister's hospital staff consisted of a House Surgeon, three Clerks and six Dressers, each serving for six months, and chosen by examination. Three of the Dressers became Clerks, the Senior Clerk was privileged to act as locum for the House Surgeon, and from among the Clerks the House Surgeon for a future six months was eventually selected.

Before entering for a Dressership I started in October, 1887, attending as regularly as other hospital duties permitted, Lister's weekly Clinical Lecture and operations. In that year Lister had discontinued using the carbolic spray.

Referring to my old notes I find that the first Clinical Lecture which I attended was on October 19th, 1887, and it dealt with a suppurating hip joint in a child; pus was evacuated and an antiseptic dressing applied,

with long splints to secure rest in the best position. The second Lecture dealt with a cured Psoas abscess in a man who had been lying in the ward for two years ; and I attended other Lectures on various subjects.

In 1888 I became a Dresser and, of course, attended Lister's clinics and operations regularly. In that year he first introduced the double cyanide of mercury and zinc gauze fixed and tinted with mauvine chloride, and he brought the first supplies for current use with him. This proved the most efficient dressing and was generally adopted by 1889.

The first Lecture of the course dealt with a pistol wound of the foot, three days old. The septic wound was freely opened, damaged bone removed, and pure carbolic acid thoroughly applied. Subsequent healing was uneventful. On that occasion Lister alluded to his experiment showing contraction of an artery in the tarsus of a horse on elevation of the leg, and the advantage of elevation of a limb before applying a tourniquet. Succeeding Clinical Lectures included tumour of the tibia ; strumous knee ; amputations ; ankylosis of the hip-joint in adduction and flexion for 11 years ; compound fracture of tibia and fibula in both legs due to a fall at the Royal College of Surgeons, dressed with 1-20 carbolic, temperature 101 degrees F. the day after the accident, but falling thereafter ; cleft palate ; surgical emphysema of chest from being run over ; gummata ; fractured skull ; intracapsular fracture of neck of femur ; the administration of chloroform ; harelip showing successful results of operation ; scirrhus of breast and importance of clearing the axilla ; inflammation ; "Lister's" amputation of the thigh for senile gangrene in a male *æt.* 76 with atheromatous arteries ; bursitis patellæ ; transverse fracture of patella caused by jumping off a cart, where there was swelling and effusion into the joint and fragments were of about equal size. Owing to the uncertainty of a good result in these cases Lister reminded us that, some years before, he had discussed with Sir Hector Cameron, a great friend and old House Surgeon, and his successor at Glasgow, the advisability of wiring these transverse fractures, opening a joint having become safe with antiseptic methods. The first patella fracture came under Cameron's care, whilst Lister wired the first fractured olecranon. Both cases were very successful. At first the ends of the silver wire were left hanging out for later removal, but afterwards the ends were left in to strengthen union, being cut short and hammered down. Lister mentioned a case where the patient was driving a four-in-hand without ill results four weeks after operation ; but not, he added, on his advice. In this connection I would mention that contemporaries of mine who were candidates for final surgery examinations were shown cases of transverse fracture and asked the treatment. When wiring was suggested by the candidate he was asked if he had personal knowledge of any cases that had been wired, and when he gave an affirmative reply he was asked the result and then the name of the venturesome operator ; who, it had been suggested by some, deserved prosecution in the event of a stiff leg, amputation or death.

In demonstrating a case, Lister was always most gentle, considerate, and sympathetic with the patient, and he continued the discussion in further detail after the patient had withdrawn from the theatre. His audiences were rarely large, although the amphitheatre was commodious, and sometimes consisted of few more than his own staff and some seniors, as well as foreign medical men, Americans, French, Germans and Japanese.

The scientific way in which the cases were presented and discussed was an education, but the Lectures did not appeal to those cramming for College and University examinations. Lister regretted this very much and would refer to the crowded attendances he used to have at his Clinical Lectures in Edinburgh.

A Clerk's six months' service was divided into two months' accident duty, two months in charge of instruments, and two months giving anæsthetics. The only anæsthetic given was chloroform, administered from a towel folded round at the edge to reach from the root of the nose to the point of the chin, at the sides just extending to the cheeks, domed to cover but clear the nose and mouth, and gathered together at the base of the fold by a large safety pin. The mask was increasingly moistened with chloroform from a drop bottle; it was raised some inches above the patient's face at first, and gradually brought down nearer; as the patient became gradually unconscious the mask was slowly raised to admit more air, whilst the chloroform saturation was diminished. All the time the breathing was closely watched, the lower jaw was just supported with a finger and the proper degree of anæsthesia just maintained. In a long case, if the mask became soggy, the Clerk could easily improvise a fresh one, and he always had a pair of catch forceps handy, often attached to the lapel of his coat, for drawing the tongue forwards in emergency. In training his Clerks to procure and maintain smooth and reliable anæsthesia, Lister did a notable service and undertook great responsibility. His constant warning was to give sole attention to the patient and not to anything else, and he would add "never speak to the man at the wheel" who steers the patient through the operation.

I gave a message of remembrance from a former Edinburgh Clinical Clerk of years before, whom I had met on a holiday. Lister remembered him and then added that there was nearly an accident once when this Clerk was giving chloroform and watching the operation instead of the patient's breathing which had stopped. An example of Lister's memory of an incident of dangerous inattention.

The "Instrument Clerk" had to put out those instruments needed on Operation Day in a large tray of 1-20 carbolic, at least an hour before operation time, and personally hand them to Lister as required, returning them to the tray when handed back. In the rare event of an unexpected need for some instrument not in the tray, it had to be dipped in pure carbolic and then passed through the 1-20 before use. The Instrument Clerk's hands sometimes became rough, numb and sore from the carbolic.

When operations were over, the instruments were thoroughly scrubbed with soap and hot water and carefully dried. The night before an operation the operation field was thoroughly washed and scrubbed and a double cyanide of mercury and zinc gauze compress, steeped in 1-20 carbolic, applied. This was removed in the theatre, the area again washed with 1-20, and towels wet with 1-20 placed around. To keep the wound irrigated during operation 1-2,000 perchloride of mercury was used. Marine sponges, which had not then been replaced by gauze swabs, were used with 1-2,000 perchloride, and stored, after being thoroughly washed and dried, in 1-20 carbolic.

Where there was undue tension in bringing the edges of a large wound together, stitches of relaxation with silver wire and lead buttons were used, the stitches of apposition being of silk, gut or horsehair. The wound was dressed with the double cyanide gauze, that next to the skin being moistened with 1-2,000 perchloride, and a layer of antiseptic wool being placed under the bandage. By these methods aseptic results were uniformly obtained. No sterilised masks, overalls of gloves were used, coat and shirt sleeves were rolled up, the juniors removing their coats; Lister buttoned up his coat, and turned up his sleeves and collar. Sometimes he removed his coat and had a sterilised towel pinned in front of him. All hands were sterilised, after washing by immersion in 1-20 carbolic. Clerks and Dressers always sterilised their hands in carbolic on entering one of the wards for duty.

We know that Lister in his long search for the most efficient dressing for wounds tried impregnating gauze with various chemicals. It is amusing although perhaps rather flippant to recall that the different tints gave a hospital humorist inspiration for the following :—

“ First there was a yellow one, then there was a blue,

“ Next there was a red one, and a white one too,

“ Now there is a violet one, and so along we go,

“ All through the colours of the bright rainbow.”

The yellow was carbolic, the blue sal-alembroth, the red biniodide of mercury, the white perchloride, and the violet double cyanide of mercury and zinc, fixed and tinted with mauvine chloride.

Special occasions brought a large audience to the theatre, as when Lister was lecturing on and demonstrating the use of Koch's tuberculin, which it was hoped would cure tuberculosis, besides being a valuable diagnostic agent.

By that time, 1890-91, I had become Lister's House Surgeon and I well remember that the wife of one of our Honorary Physicians came to ask me just before Lister was due at the hospital if I thought he would mind if she was amongst the audience. I told her that I was extremely doubtful but asked her to wait in the ante-room of the theatre. I met my Chief on the steps, as he alighted from his carriage, and when we had crossed the entrance hall to my sitting-room I told him. He sighed, as he usually



did when disturbed or irritated, and on his way to the theatre he passed into the ante-room, and taking one of the lady's hands between both his, he begged her to excuse him, for he had never given a Surgical Lecture-demonstration before a mixed audience, and he would not feel at his ease if she were the only lady and non-medical, amongst a large number of medical men and students. It was with a sigh of relief that he bade her farewell and passed into the crowded theatre to give his Lecture-demonstration.

I was extremely fortunate in getting a total of 10 months' experience as Lister's House Surgeon owing to the illness of my predecessor. No man has so impressed me, and since I served him to this day I have had a signed portrait of him in my room. He has been so well described by others that I can add little. He was erect, five feet ten inches in height, and well built, dignified and grave, with a noble head, straight nose and fresh complexion, clean shaven except for side whiskers, grey hair parted on the left and worn long and curly around the neck. The left angle of his mouth was drawn up a little. His voice was quiet and gentle with occasional slight stammer or hesitancy in giving an address. His dress always consisted of a black broadcloth frock coat and waistcoat. The sleeves were long and rather wide, so that they could be easily turned up (this is noticeable in photographs), grey cashmere trousers, a white shirt with soft cuffs, erect collar with turned down points, and a black tie, tied in a bow. A gold watch-chain, but no rings, and I never saw him wearing gloves. Amongst the various operations whilst I was House Surgeon was one of amputation at the hip-joint by Lister's method of amputating the soft parts high up first, and dissecting out the head of the bone afterwards, which made the operation less formidable. It was a case of large sarcoma of the lower end of the femur in a boy who lived six months before dying from recurrence in internal organs.

At the commencement of a major operation I always noticed a momentary pause, with scapel in hand, and felt sure in my own mind of the significance, and that was confirmed when I learnt of the letter he sent to his sister, after his first public operation in 1857 in Edinburgh Royal Infirmary before a large number of spectators, mentioning that he subdued his nervousness by bearing in mind only one Spectator who is ever present.

He was a deliberate and careful operator and did not aim at the necessary swiftness of surgeons like Liston and Fergusson, in pre-anæsthetic days; but he could be rapid if need arose. He was handicapped by free perspiration, and a nurse had to be handy with a towel to dry his face.

He attended the hospital every day, including Sundays. On week-days he drove up and his House Surgeon met him on the steps at the main entrance; he passed across the entrance hall to the House Surgeon's sitting-room where he always deposited his hat before proceeding upstairs to the wards or theatre. On Sundays he walked in on his way home from the "Temple Church"; and visited the wards for a short tour of inspection

and to undertake any dressing he thought necessary. He dressed all operation cases himself, and on week-days he taught and demonstrated the aseptic results of his antiseptic methods. Foreign surgeons were frequently present and very appreciative of all they saw, and Lister would converse with them in French and German. He would invite those strangers present at a ward dressing to notice that the dressing he had just removed was aseptic and odourless. He never allowed himself to be drawn into any conversation on subjects not appertaining to the matters in hand and no irrelevant matters were touched upon in the wards or theatre.

I should mention that Lister's one failing was a tendency to occasional unpunctuality at hospital which was explained by his complete disregard of time when he was engaged on any important medical service. Lateness at a special lecture elsewhere, as at the Royal College of Surgeons, is said to have been due to a last-minute desire to test or clarify some detail that had occurred to him.

As I have already said he never forgot a patient's feelings, and in dressing a breast case or when removing stitches, the patient's face was turned to the opposite side and a folded towel so arranged over the head of the bed as to exclude the wound from the patient's field of vision. He taught us a life of high ideals and unstinted service. He used to say "I do not praise my assistants but I find fault with them if they do wrong."

Lister always pointed out that in the matter of bandaging a wound, it was very necessary so to place the safety pins that the dressing could not slip, or the precautions against sepsis might fail. He did not hesitate to impress this upon us by referring to his own forgetfulness of a necessary safety pin in the dressing of a wound after he had opened a large axillary abscess in the person of Queen Victoria in 1871. After he had left her Majesty he remembered the omission of a safety pin vital to the security of the dressing, and he was constrained to return and suffer the embarrassment of having to ask her Majesty to undress again, so that he could rectify the omission. In connection with this wound I also learnt that the piece of lint being used as a drain having proved insufficient, Lister, on considered reflection, decided to try, instead, a piece of rubber tubing taken from the carbolic spray apparatus, in which he cut holes at intervals, tied a silk loop at one end, and steeped over-night in 1-20 carbolic. This proved most efficient and rapid healing took place.

Lister generally performed his private operations at the same nursing home, No. 15, Fitzroy Square, and I had opportunities of helping him there and sometimes giving chloroform.

I appreciated all I learnt from Sir Watson Cheyne, Bart., F.R.S., whom Lister brought from Edinburgh to be his first House Surgeon at King's in 1877. During my hospital service I had the advantage of acting as Cheyne's House Surgeon when he undertook the care of beds in the absence of Lister.

Whilst serving with Lister I was present at a meeting in the hospital with Sir William Bowman, Bart., F.R.S., the distinguished ophthalmic surgeon of the nineteenth century, and a Member of the Council of King's College, London. Many have thought that Bowman was one of those who secured the appointment of Lister to King's on the death of Sir William Fergusson.

Lister entertained his hospital staff to dinner at his house in Park Crescent during their period of office, and then they had the pleasure of meeting Lady Lister, James Syme's eldest daughter, Agnes, who had been her husband's constant companion and devoted helpmate in all his activities since they were married in Edinburgh in 1856. I remember the hospital Christmas entertainment in 1890 when Lister brought his wife and spoke to each of his patients in turn, and it was evident that Lady Lister had previous knowledge of each case of special interest or difficulty. In little more than two years, on April 12th, 1893, she died of pneumonia at Rapallo, whither they had gone for rest and change, and Lister for the remainder of his life was "a very solitary man."

I was present at a remarkable gathering on May 26th, 1897, when Lord Lister's former House Surgeons, Clerks and Dressers gave him a banquet. I well recollect our affectionate and unbounded enthusiasm, and he was toasted in Scotch fashion. Some of those present came long distances, even from overseas.

Amongst the many honours conferred upon Lister the following are outstanding :—

In 1895 he had been elected President of the Royal Society, a position he held for five years.

In 1896 he was made President of the British Association.

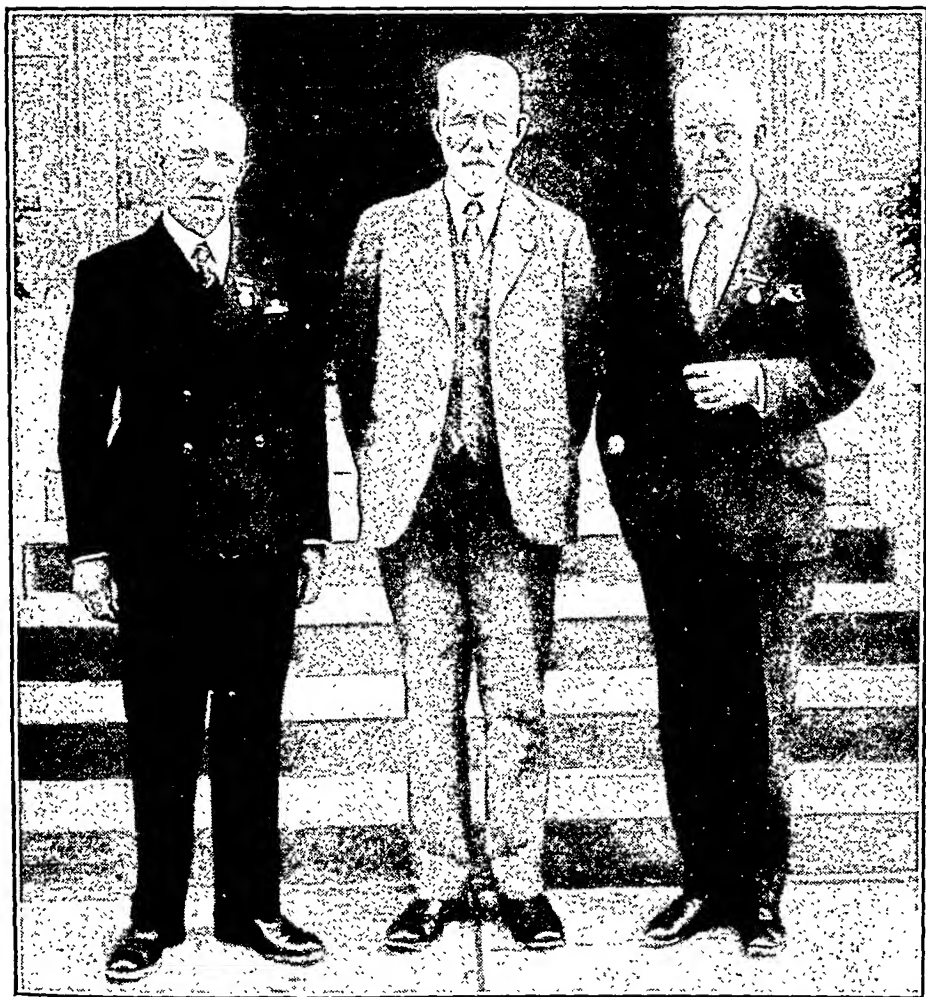
In 1897 on the occasion of Queen Victoria's second Jubilee he was raised to the Peerage.

In 1902, King Edward VII selected him to be one of the first 12 recipients of the Order of Merit; and he became a Privy Councillor.

Lord Lister died at Walmer, Kent, on Saturday, February 10th, 1912, in his 85th year, after four days' illness from pneumonia, from which disease Lady Lister had died 19 years before. Lord Lister has been termed "the father of modern surgery." To quote the obituary leader in *The Times* of February 12th, 1912, "If true worth be measured by work accomplished for the benefit of mankind, very few worthier have lived and died."

In the words of Shakespeare, "I shall not look upon his like again."

On Friday, February 16th, 1912, I remember the crowded and distinguished congregation, in which H.M. The King was represented, at the impressive funeral service in Westminster Abbey, where Lord Lister would have been buried, had it not been for his well-known wish to be laid to rest beside his beloved wife in Hampstead Cemetery. In the



L. V. CARGILL

JOHN STEWART

SIR ST. CLAIR THOMSON

Three of Lord Lister's House Surgeons—photograph taken at B.M.A. Meeting in Winnipeg in 1930.

words of the Anthem which was sung, "His body is buried in peace, but his name liveth evermore."

Some 18 years later, at the British Medical Association Meeting in Winnipeg in 1930, John Stewart, C.B.E., Sir St. Clair Thomson and I were photographed together as three representative House Surgeons of our beloved master, in that order of seniority.

John Stewart came to King's with Lister in 1877 and succeeded Sir Watson Cheyne as House Surgeon. He subsequently settled down in Halifax, Nova Scotia, and became very well known as an eminent surgeon, spreading Lister's methods and teaching in Canada.

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## A PATIENT REMEMBERS LISTER

*THERE CAN ONLY BE* few people still alive on whom Lord Lister operated. The Editor has received the following communication from one of these, Mr. J. Bond, 252, Queens Road, Richmond, Surrey. He writes :—

"When I was just over two years of age I slipped on some wet, soapy oilcloth, left in that condition by a charwoman, and injured my left hip. My parents took me to a number of London Doctors who diagnosed that the pain I felt subsequent to the accident, and the limp I developed, was due to growing pains. This, I understand, was quite a common complaint in those days, but it is now realised by all that it is not painful to grow.

"My mother was a Scotswoman and she had heard of the fame of Professor Lister in Edinburgh. She took me there, to ask him to examine me, only to find when we arrived in Edinburgh that he had gone to London to take up a new appointment. We went back to London and I was taken to see Professor Lister. He diagnosed that I had developed inflammation of the hip joint as a result of the injury and advised an immediate operation. This first operation was performed in King's College Hospital, and the 13 subsequent ones were performed either in the University College Hospital or in his private hospital, Fitzroy Square.

"My recollection of the appearance of Lister during the long period I was under his care, is that he was an extremely benign man, with a kindly smile. He instantly inspired confidence in me and his touch, which was most gentle when he examined me, was like a caress. He was usually clad in a long black frock coat which was the professional uniform of that period. I still remember the dread I felt when one of his assistants examined me, instead of himself. I used to cry out with terror as I realised the touch and examination by his assistant would not be so gentle as that of his chief.

"Finally, Lister told my mother that he could do nothing further for me by means of operation, but he assured her that with careful nursing

at home the operation wounds might heal and ultimately complete recovery be achieved.

"I know that my recovery was due to my mother's constant loving care which supplemented the knowledge and skill of one of our greatest surgeons.

"More than four inches of diseased bone were removed from my left thigh bone and I well remember the continual dressing of the wound which my mother had to carry out, and how she had to change the red rubber drainage tubes, and moisten the dressings with dilute carbolic acid.

"The result of these operations was that my leg became very much shorter than the other, though, when I was bed-ridden, weights were attached to my leg in order to draw it down as much as possible. I remember vividly on one occasion crawling out of my bed and reaching the far end of the garden with the weights still attached to my leg.

"At the present time I have 12 inches of shortening of my left thigh bone and it was not until I was between nine and 10 years of age that I was able to get about and learn to walk with the aid of crutches. I am now able to wear a suitable prosthesis and so conceal the extent of my deformity. Ever since I was a child I have had excellent health, I have seldom had to consult a Doctor and up to quite recently, with the aid of a stick, I was able to walk 10 miles at a stretch.

"What I might call Lister's 'autograph' consists of a series of scars due to the various operations which he performed around my hip joint. Some of these scars are fixed to the deeper tissues and indicate the position where the drainage tubes were placed. I find I occasionally get some inflammation in the neighbourhood of one of these scars.

"My memories of the hospitals where I spent so long a period of my childhood are still very vivid. Ever since my first operation I have loathed the smell of carbolic acid. It always conjures up the vision of a nurse walking slowly about the ward working a bright copper spray which was meant to disinfect the air. I have heard medical men say that the occasional occurrence of hospital gangrene is due to the fact that the air is no longer disinfected by carbolic acid. I also dislike carbolic soap so much so that I am unable to occupy a room in which it is kept. The pink colour of carbolic powder also upsets me in the same way; in fact anything pink in colour, even the petals of cherry blossom, brings back memories of my operations. Medical men should realise the importance and effect produced by impressions on the mind of a child.

"The anæsthetic used for these operations was usually chloroform and I still remember the curious psychological effect it had on me during my recovery from the anæsthetic. It usually consisted of a dream. I was always in the middle of a large field, just below a windmill on the skyline and hundreds of sheep were racing past me. The dreams of most people are monochrome, but mine have always been in colours.

"I fully realise if X-rays had been discovered before my illness I might have been relieved of great pain and a good number of operations. The diagnosis would have been very much more easy and my deformity would probably have been very much less. I do realise, however, that radiography can never take the place of clinical surgery in making a correct diagnosis, it can only be used as an adjunct.

"It is very lamentable that the present generation in this country knows little or nothing of Lord Lister's work and devotion to the service of humanity. His discoveries must have saved many lives throughout the world yet many have never even heard his name. On the other hand the name of Pasteur is well known, probably due to what is known as the pasteurisation of milk and also recently by seeing the superb film entitled 'Pasteur.' Surely a film illustrating the life and work of Lord Lister is long overdue. Not only would it bring prestige to British science but would also greatly profit the cinema industry.

"In Florence in 1912, that is the year Lister died, an Austrian Doctor told me that Britain's contribution to medicine was insignificant and that the German race were far ahead of any other in medical science. Surely there is enough material in the life of Lister and his achievements to make a film which would interest everyone. It would at least be as dramatic and stimulating as that of Pasteur. Surely now is the time for such a film to be made and shown as the import of films from America has now ceased. It can be summed up by the words of the American Ambassador who, when proposing the health of Lord Lister at the jubilee of his Doctorate, said: 'My Lord, it is not a profession, it is not a Nation, it is humanity itself which, with uncovered head, salutes you.'"

# HARE-LIP

by

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TO COVER THE SUBJECT of hare-lip fully it would be necessary to discuss first all the different varieties of the deformity and secondly the different methods of operating. This is obviously impossible in a lecture of this kind. In consequence, I must confine myself to one variety of hare-lip, the severest degree with a double cleft and a displaced premaxilla : and then describe solely my own methods of operating. Yet, since the type of deformity discussed unites in itself all the lesser degrees of the same condition, to describe it does, to a very fair degree, describe them all. And those who are likely to read this paper with real interest will be as familiar as I am with the various techniques I have discarded or modified.

## THE ELEMENTS OF THE DEFORMITY OF COMPLETE DOUBLE HARE-LIP

1. *The failure of development of the columella.* The tip of the nose, instead of standing right out from the skin of the lip, as it should normally do, is almost on a level with it. The columella, or free anterior end of the nasal septum, is thus abnormally short. But it should be remembered that in babies the normal columella is very much shorter in proportion than in the adult, and the force that stretches it as the button nose of the baby turns into the prominent pointed adult one is also active in these hare-lips. If the tip of the nose is left free while the lip is pulled back into proper position, the forces thus set up will stretch the columella into quite a fair length. I think it is a grave mistake to try to lengthen it by putting into it skin that belongs to the lip.

2. *Failure of development of the labio-gingival sulcus.* In contrast to the first element of the deformity described, this important but not very obvious one has no tendency to correct itself. The central portion of the lip is stuck down upon the underlying bone of the premaxilla. If this is not freed there are several bad consequences :

- (a) As the lip is fixed in the centre it is immobile and expressionless.
- (b) It is extremely difficult to fit a dental plate in later life, and owing to the interference with dentition, most of these cases will need one.
- (c) It prevents the proper joining of the ends of the muscle of the oral sphincter. In my technique this is of great importance.

If this sulcus is not constructed as a first stage in the operation it will need some most difficult skin grafting much later in life. However successful this may finally be, the muscles will never have developed well,



owing to their immobility during the most important time of growth. To construct it, advantage is taken of the way in which raw surface surrounded by mucous membrane will epithelialize quickly and without contraction.

3. *Displacement forwards of the premaxilla.* For some mysterious reason, when there is a cleft of the gum new bone begins to form in front of the vomer, between it and the premaxilla, so driving the latter forward. The vomer itself does not grow, and the division between it and what may be called the "pre-vomerine bone" is marked by a cartilage-filled suture line (Fig. 1).

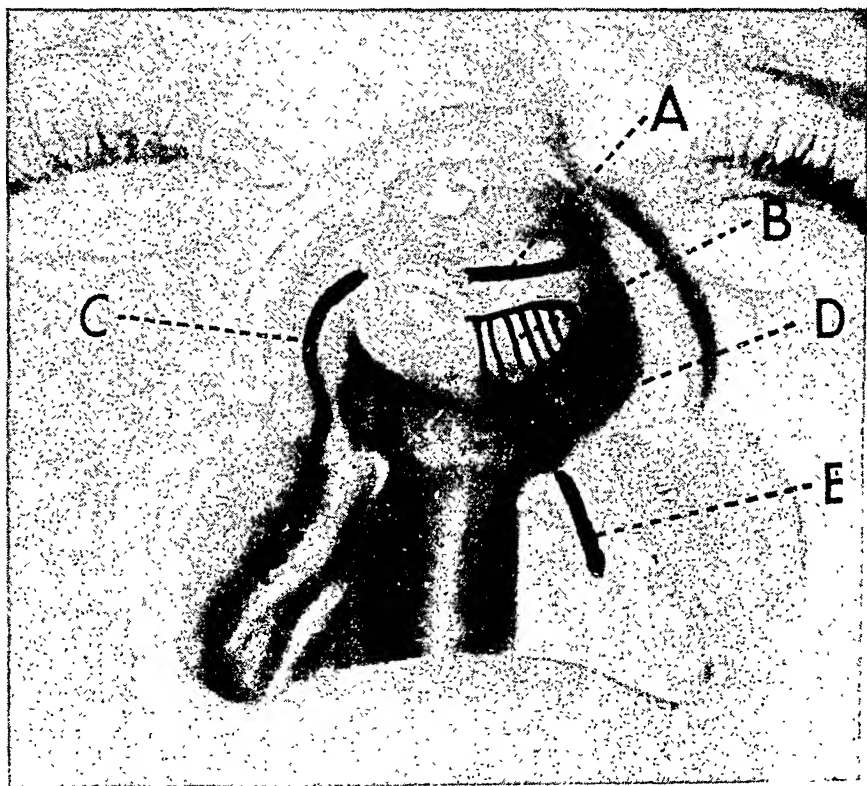


Fig. 1. View of complete double cleft lip from below. A—Line of incision to cut central portion of lip free from premaxilla. B—Area to be made raw in order to fuse with flap of muco-periosteum. C—Line of incision to free nostril. D—Bulge showing suture line between vomer and pre-vomerine bone. E—Line of incision to turn down flap of palatal muco-periosteum.

If the premaxilla is not placed in its normal position and firmly fixed there the consequences are :

- (a) Great difficulty in joining the lip over it, so that it is usually advised to do only one side at a time.
- (b) A very ugly profile, as the protrusion of the bone under the upper lip gives an animal-like snout.
- (c) Great difficulty in fitting dentures, as in addition to being too far forward, the central portion of the gum is very wobbly.

It is sometimes said that if the lip is joined over the premaxilla it will come back into position. I have never seen this occur and I have seen many cases in which it has not occurred. There is no explanation of where the pre-vomerine bone would go to if the premaxilla did go back, and in any event there would still be the trouble of its mobility. Replacing the premaxilla has got a bad name because of the erroneous way in which it has been carried out in the past. To get a good result one must :

- (i) Remove only the pre-vomerine bone that pushes it forward. If a wedge is taken out of the vomer, as was usually advised, the foundations of the nose are ruined and it goes flat on the face.
- (ii) Cut the premaxilla free from the nose and the central part of the lip which adheres to this. If this is not done the tip of the nose is obviously dragged back.
- (iii) Get actual junction between it and the alveolar ridge ; on both sides for preference, but on one at least. Sometimes the gap is so wide that it is impossible to get the displaced portion to touch both sides at once, and the result is then like a complete single hare-lip. If this junction is not gained, the bone will often atrophy in a surprising manner, so that one would imagine it had been excised. When properly replaced the premaxilla often grows a pair of surprisingly good central incisors ; but this cannot be depended upon.

4. *The cleft of the floor of the nostril.* There are two elements in the displacement that occurs here. The first is the obvious lateral shifting that produces the wide gap. But in addition to this there is a displacement caudally or downwards of the outer end of the ala of the nose that must be corrected at the same time. There are three main points to be observed :

- (a) The natural tendency in closing a gap of this kind is to sew any point on one side to the point on the other side directly opposite. It is this that produces the typical drooping of the nostril on the outer side of a mended hare-lip. A far better nostril will be formed by sewing a short piece of skin that appears to belong to the lip just to the outer side of the nostril to a corresponding raw edge lying inside the nostril on the nasal septum.
- (b) In freeing the nostril and cheek from the underlying bone it is a mistake to cut inside the nose in such a way that the whole

outer side of the nostril is brought in. If this is done the thick posterior part of the nostril will swing in and obstruct the airway. The incision on the inner side of the nostril should run quite close to the skin edge, leaving the posterior part of the ala in its original place adherent to the maxilla.

- (c) The gap in the bone needs a force to pull it together, and this can be supplied by the contraction in healing of the raw undersurface of the floor of the nostril that is left by a simple joining of the surface. If a mucous lining for the deep surface is constructed at the same time this force is much weakened.

5. *The cleft of the lip.* In joining the lip I make two assumptions. The first is that the best way to join the lip will be to imitate the manner of junction that should normally have occurred. The second is that as muscles are involved in the cleft, and their correct post-operative action is necessary for a good result, these muscles should be treated according to the orthopædic principles established in managing similar muscular gaps elsewhere. To imitate the normal function of the lip involves first finding out what it is: the two straight vertical lines of the anatomy books have obviously no connection either with the moulding of the normal lip, or with the curious shape of its elements found when these fail to fuse. I think the key to it is to be found in the central papilla which is so plainly noticeable on the lip of a baby, though on an adult it has usually disappeared. On turning up the lip this papilla will be seen to be the tip of a shield-shaped area outlined by a groove on the mucosa, suggesting that the enclosed space is all that remains of the undersurface of the central portion. If this is correct it means that the central portion has no part in the formation of the mucocutaneous line.

The philtrum, that vertical groove down the centre of the lip, is outlined by two ridges. I assume these to be caused by the over-riding of the thick lateral portions over the thinner central one. This over-riding naturally goes farthest where the two parts first meet, at the upper part of the line of junction, and in consequence the space between them, that is to say, the groove of the philtrum, is there narrower than below. Now it is obviously impossible to imitate this process exactly, but three main principles emerge from consideration of it:

- (a) No skin of the lateral portions meets below the central portion.
- (b) The central portion forms no part of the red margin.
- (c) The muscles meet and join under the skin of the central portion.

The correct surgical formula should observe all these principles. It is worth while considering here what are the properties of the ideal human lip to which the one surgically formed should have as much resemblance as possible. According to present conventions of beauty it should be:

- (a) Short from above downwards.
- (b) Thick antero-posteriorly.
- (c) The red margin should be loose, rounded, and slightly everted.

(d) There should be a well-marked double curve or cupid's bow in the line of the mucocutaneous junction.

(e) The lip should be mobile in speech or expression.

It is hardly necessary to point out that the formulæ given in many textbooks for joining the lip do not observe the principles laid down, and cannot possibly produce a lip of the kind desired.

## THE TECHNIQUE OF OPERATION

*Preliminary operation.* The object of this is to get the premaxilla firmly fixed in its correct position and to construct a proper labio-gingival sulcus.

*Time of operation.* It should be performed about three months of age, and an interval of about a month should be allowed between it and the joining of the lip.

*Anæsthetic.* This should be intra-tracheal gas and oxygen. The child should be bandaged to a light wooden crucifix, which by preventing movements will enable the degree of anæsthesia to be kept extremely light. This is important as there is a considerable unavoidable loss of blood, and with deep anæsthesia shock may be dangerous.

*Instruments.* No special ones are needed beyond the little spiked plate, to keep back the premaxilla, and a chisel-knife. The surgeon's ordinary technique of sewing with a needle-holder should carry him through this operation as well as that for a cleft palate.

### *Steps of operation.*

1. Cut the soft tissues of the lip away from the premaxilla. This should be done very thoroughly, the division being carried right back to the nasal septum. Two arteries on the lifted flap need catching with artery forceps, which serve to pull it away from the subsequent manœuvres as well as to stop the bleeding.

2. Make a longitudinal cut over the pre-vomerine bone, and remove it sub-mucously with narrow biting forceps. This should allow the premaxilla to be forced straight backwards into the normal line of the gums. It is preferable to leave it a little too far forward rather than to force it too far back.

3. With an awl carry a stitch of very strong silk-worm gut or nylon through the alveolar ridge on either side of the gap. Bring this through the holes in the spiked bar, force this bar into the narrow upper part of the raw surface of the premaxilla, and tie it so that this is fixed firmly in position. A further loop of the suture is made round the bar and through the septum of the nose; and when this is tied the bar cannot drop downwards.

4. Cut the mucosa off the posterior and lateral sides of the premaxilla with a small sharp knife. This is to give a raw surface to which the flaps cut in the next step can adhere.

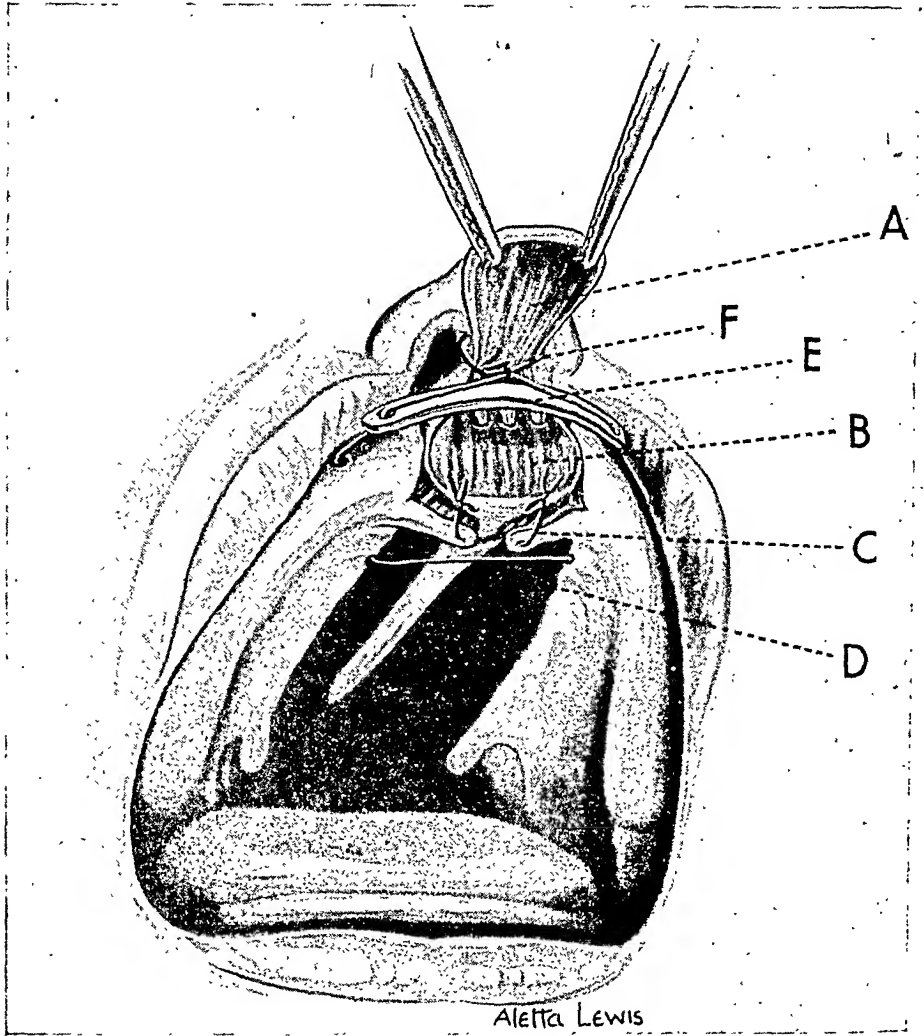


Fig. 2. Completion of the operation for replacement of the premaxilla and construction of the labio-gingival groove. A—Raw undersurface of central portion of lip, cut free from premaxilla. B—Raw surface corresponding to A. C—Flap of muco-periosteum turned down off anterior angle of hard palate, and sewn to a patch made raw on the posterior aspect of the premaxilla. D—The stitch fixing the retaining bar through the alveoli. E—Retaining bar, with its spikes driven into the bone of the premaxilla. F—The loop of the suture tying the bar to the nasal septum.



Fig 3. The central portion of the lip has been cut free from the premaxilla. It is held away from it by the stainless steel plate that keeps the premaxilla back in position while it fuses with the edges of the alveolar cleft.

5. Raise the anterior ends of the muco-periosteum of the hard palate as flaps, lever them backwards and inwards so that they come against the raw surfaces on the premaxilla, and stitch them there with fine linen sutures.

6. Leave the plate in position for a fortnight if possible, though it may become too loose to be effective after 10 days.



Fig. 4. Profile view before operation showing the lack of development of the columella and the labio-gingival groove



Fig. 5. Showing the effect of the primary operation in freeing the central portion of the lip and getting the premaxilla into normal position without pulling back the tip of the nose.



Fig. 6. Showing a replaced premaxilla firmly fixed in the correct position and growing two apparently normal teeth at the correct angle.



Fig. 7. Showing the premaxilla back in position. Note the narrowness of the gaps on either side after this, with consequent lack of tension after joining. A—Line of incision to make raw surface to sew to septum just inside nostril.



The result should be as shown in Figs. 4, 5, 6 and 7, with the pre-maxilla firmly in position and its upper surface, which was made raw, covered all over with oral mucosa. One disadvantage of this technique is the possible damage done to the tooth germs by the suture which is brought through the alveolar ridge. How dangerous this is I do not know, but in any event the upper teeth in these cases are going to be defective.

## SECOND OPERATION

The final stage in correcting the deformity is to join the floor of the nostril and the lip itself. Its stages are :

1. Put in tight temporary sutures of linen to control the coronary arteries on either side. These should be passed just inside the angles of the mouth, to catch the artery which can be felt running just under the mucosa. They are far more effective and less hindrance to the operator than the various forceps designed for the purpose, and can save a good deal of the bleeding in what is unavoidably a rather bloody operation.

2. Free the whole cheek and ala of the nostril from the underlying bone. This can be done very rapidly with dissecting scissors and the arterial bleeding so caused controlled by an assistant pressing on the cheek for a few minutes while the surgeon continues with the next step. In freeing the nostril the cut should be taken close to the edge of the ala, as has been already advised.

3. Cut down the mucocutaneous junction on the lip for about a quarter of an inch below the nostril. This gives a raw surface there which is to be sewn to the septum.

4. Make a raw edge on the septum by cutting backwards from the opening of the nostril and removing all the mucosa below this. This edge should run along the normal line of the floor of the nose.

5. Bring the two raw edges so made together by a linen mattress suture. This form of suture is used because there is no need to avoid scarring on this surface, and this is one of the points at which tension is unavoidable.

6. Put in some very fine adjusting sutures to bring the edges together microscopically.

7. Cut the central portion of the lip into a V, and remove all the mucosa from its undersurface. I find this is the step in the operation which arouses most opposition ; especially to those who have had to do with war wounds it seems madness to sacrifice so much tissue and so much surface. But it should be realised that though most plastic surgery is concerned with conditions in which there is too little surface, there are other conditions in which there is too much. If this ruthless cutting is not done, the geometry of the junction will not work out, and it will be impossible to join the muscles properly.

The cutting is done in the way that saddlers from time immemorial have cut the very similar substance of leather, by forcing a sharp blade



Fig. 8 Showing the stitching of the floor of the nostril. A linen mattress suture joins the skin just outside the nostril on the outer side to the mucosa on the septum just within it.

through it on to a piece of soft wood held underneath it. The blade is shaped like a chisel and should be razor sharp. In this way one gets a perfectly straight cut at right-angles to the surface, and avoids the difficulty of holding and cutting the extensible and slippery lip tissues, which alter shape as a cut proceeds.

8. Cut the lateral portions of the lip for suturing. For this it is necessary to keep all the red margin, but to allow this to be adjusted round the lower angle of the central V in such a way as to produce the "cupid's bow" double curve that has been mentioned. This is done by pushing a 2 mm. ophthalmic trephine through the lip at the level of the tip of the central V, placing the circle with care so that the mucocutaneous line forms a tangent to it. The trephine hole is then connected to the raw surface sewn to the septum by a cut with the chisel-knife. This produces a kind of hook of red margin, which is then trimmed by cutting off the small strip of skin left upon it by fine scissors, as well as any tags of mucosa. These two hooks of red margin are then pulled downwards by a stitch which is passed through them, to give the effect shown in Fig. 10. Experiment with leather or other similar substance will show that, when it is desired to change suddenly the direction of a cut, the smallest segment of a circle at the point of change enables this to be much more easily done, and the whole raw surface to be flattened out, than if two cuts were allowed to meet at a simple angle.

9. The suturing turns upon one unexpected stitch, which continues the lifting-up process begun by the formation of the floor of the nostril. This stitch enters the lateral portion opposite the trephine hole: but instead of being taken across in the obvious way to the corresponding

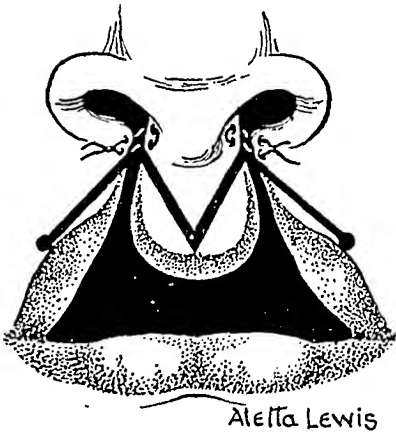


Fig. 9



Fig. 10



Fig. 11

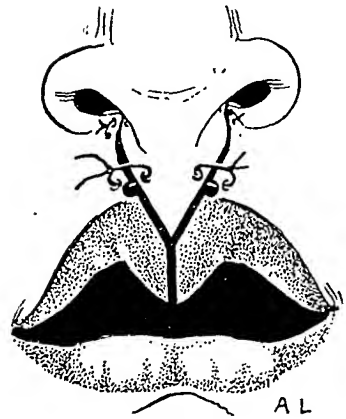


Fig. 12

Fig. 9. Showing the cutting of the lip. The trephine holes are made level with the tip of the V into which the central portion has been cut, and are connected to the raw surfaces stitched to the septum by cuts with the chisel-knife. The strips of skin attached to the hooks of mucosa thus formed are trimmed off with fine scissors.

Fig. 10. The appearance when the hooks are held down by a temporary stitch and the first stitch is inserted. Note how it slopes acutely downward from the centre of the side of the central portion to the trephine hole on the mucocutaneous border.

Fig. 11. The first crucially important stitch is tied. Note how this bends the mucocutaneous line in such a way as to form one half of a cupid's bow.

Fig. 12. The eventual shape of the lip defined by the two primary sutures. All that is now needed on the anterior surface of the lip is fine adjusting sutures.

trephine hole, which lies invitingly opposite, it is passed through the middle of the side of the central V. One of the most dramatic moments I know in surgery is when the insertion of this stitch and its fellow on the opposite side suddenly pulls the whole rather alarming collection of raw surfaces together and produces from them a very reasonable looking lip. Once these two stitches are in place it is only necessary to put in fine adjusting sutures to complete the sewing of the external surface of the lip.

10. The joining of the muscles is done by deep vertical mattress sutures of 000 chromic cat-gut, inserted so as to bring together the whole thickness of the lateral portions with the exception of the already sutured skin. The first of these is put in opposite the trephine holes, and two others usually are enough to join the entire undersurface of the lip. The effect of these sutures is treble: to join the muscles, to join the mucosa, and to make the lip pout so that the red margin is everted in the way that has been laid down as desirable. There is no need to dissect the muscles free and suture them as a separate layer. One knows exactly where they are, and the less they are injured the better.

11. A tension-bridge, or modified Logan's bow, is then placed in position and tightened up to its fullest extent. The original Logan's bow was a static device that simply prevented the sides of the wound falling apart, and often failed to do this owing to the inevitable slipping and stretching of the sticking-plaster that held it. The tension-bridge, on the other hand, has a dynamic action in actually forcing the raw surfaces together as a carpenter clamps together two glued surfaces of wood. Its effects are:

- (a) To avoid the breaking down of the wound. Several thousand successive cases have been done without this occurring.
- (b) To avoid stitch scarring, as may be seen from the photographs, even though the stitches are left in longer than usual. It is tension upon a stitch that makes it mark, rather than the time it is left in.
- (c) To observe the orthopædic principle of allowing newly joined muscles to heal in the position of contraction. If the lip is to have the power of voluntarily pouting after operation, as it should have, it must be held in the position of pouting, that is contraction of the oral sphincter, during healing.

12. Penicillin and sulphonamide powder is then blown on to the wound. This mixes with the slight exudate present at this stage to form an antiseptic scab, which should stay dry and hard throughout healing. No other dressing is used.

13. The stitches are removed at six or seven days. This should be done by the surgeon himself as it is far from easy owing to the resistance of the baby. Clumsy removal may open the wound.

14. The tension-bridge is left in position for another week, and then removed.



Fig. 13. Case before operation.



Fig. 14. Same case as Fig. 13 after the two operations described.

# HARE-LIP



Fig 15 Case before operation



Fig 16 Same case as Fig. 15 after the two operations



Fig 17. Case of displaced premaxilla with double hare-lip after two operations.

## RESULTS

These are shown by the photographs. It must have struck anyone who has studied the literature of the subject how extremely difficult it is to find a photograph of a result from a complete double hare-lip which really shows what one wishes to know. I would suggest laying down certain rules for such photographs :

- (a) The scale of the reproduction must be at least a third of the normal, preferably larger. A photograph the size of a postage stamp is very little use.

## HARE-LIP



Fig 18. Case of displaced premaxilla with double hare-lip after two operations.

- (b) The focusing must be as hard and definite as possible; the separate hairs of the eyelashes should be distinct. The slight haziness of outline suitable for a social portrait is out of place here. This means that the scars will show: if they do not, the picture is of very little interest to a surgeon. I believe it is only possible to get this definiteness in babies by a flashlight technique.





Fig. 19. Case of displaced premaxilla with double hare-lip after two operations.



Fig. 20. Case of displaced premaxilla with double hare-lip after two operations.



Fig. 21. Case operated upon after a formula still to be found in many textbooks.

- (c) The patient should not be smiling, as this stretches the lip and flatters the result by doing away with irregularities.
- (d) No make-up should be used on the patient and no retouching done to the pictures. A study of illustrations in textbooks of plastic surgery will show that this rule is far from unnecessary.

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I should like to thank Mr. Derek Martin, Assistant Curator, The Hospital for Sick Children, for his patience and technical skill in taking the photographs illustrating this article.

## "OBSERVABLES". AT THE ROYAL COLLEGE OF SURGEONS

### 21. A SILVER SHAVING SET

A MOST INTERESTING addition was made to the collection of plate in the College when Professor Evelyn Sprawson, M.C., F.D.S.R.C.S., presented to the Faculty of Dental Surgery in May, 1949, a silver shaving set. Being complete with bowl, jug, and soap box, this set is very rare, if not unique. It was made in 1751 by Edward Wakelin, and bears the arms of George William, sixth Earl of Coventry.

It is interesting to note that this silver dates back almost to the time when the united Company of Barbers and Surgeons was still in existence, and although recently acquired, it is among the oldest of the College silver, being of only slightly later date than John Hunter's tankard (1738), the Ranby Cup (1745), and the Cheselden Cup. K.C.

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### SAYINGS OF THE GREAT

"A moment's insight is sometimes worth a life's experience."—*Oliver Wendell Holmes*. (Submitted by Professor Lambert Rogers.)

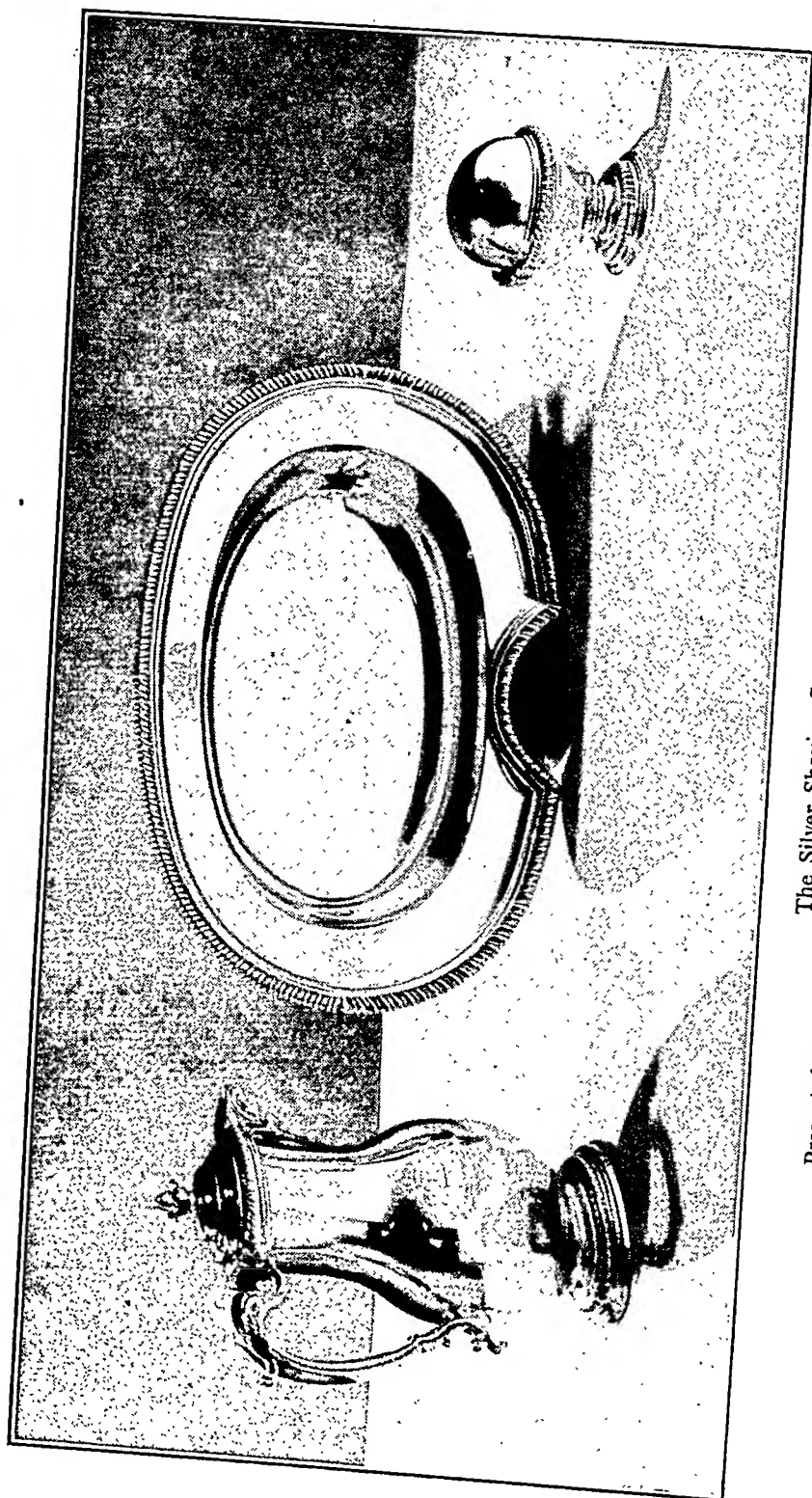
"It is most important both for happiness and for duty that we should habitually live with wise thoughts and right feelings."—*J. Morley*. (Submitted by Ronald W. Raven, O.B.E., F.R.C.S.)

"An event experienced is an event perceived, digested and assimilated into the substance of our being."—*Wilfred Trotter*. (Submitted by C. Allan Birch, F.R.C.P.)

"The more urgent the call for decision and action, the more important are character, the slowly matured power of judgment and a grasp of fundamental principle, and the less trustworthy are mere detailed knowledge and executive skill."—*Wilfred Trotter*.

"Both sides wistfully acknowledge that the whole truth about the Universe cannot be discovered in the laboratory or divined by the Church. But where it can be found is a more difficult matter to determine."—*Trevelyan*.

"A man must carry knowledge with him if he would bring home knowledge."—*Johnson*.



The Silver Shaving Set  
Presented to the College by Professor Evelyn Sprawson, M.C., F.D.S.R.C.S.

# AMPUTATIONS, LIMB FITTING AND ARTIFICIAL LIMBS

Lecture delivered at the Royal College of Surgeons of England

on

11th April, 1949

by

Dr. A. W. J. Craft, O.B.E.

P.M.O., Ministry of Pensions, Research Department

AMPUTATIONS AND AMPUTATION sites have been described in surgical textbooks over a number of years and modifications and variations of what are termed ideal or standard amputation sites have been suggested in very many instances. The result is that difficult problems are left to those called upon to prescribe a prosthesis and to those who have to make it; apart from the fact that the comfort of the patient has been in many instances of secondary importance. It has been said, much too often, that a skilled limb-fitter is able to make a prosthesis for any type or site of amputation. Experience gained during the past 30 years has proved quite conclusively that certain lengths of stumps, the position of the scar, and the general surgery of amputation all materially assist an amputee in being free from subsequent surgery. The design and mechanism of the integral parts of artificial limbs, together with the all-important question of proper fitting and correct alignment have been studied in a detailed manner over a period of years. If, then, the artificial limb has received such careful study to ensure satisfactory fitting and efficient use by the patient, why should not the surgery and site of amputation be more standardised? We should have a properly shaped stump of ideal length with the scar in the position best suited to the limb which will be worn. Such cooperative work between surgeons, limb manufacturers and all others concerned in the welfare of amputees will materially assist in the work of rehabilitation of the disabled.

From a wide experience gained by examining all classes of amputees attending Roehampton from hospitals throughout the country one is astonished at the various lengths of stumps, the irregular and bad position of scars, the superfluous muscular and even fatty tissue left in the stump, the flexion deformities and other stump conditions. The good results appear to be those carried out, and cared for post-operatively, by orthopaedic surgeons. When the question is asked as to why amputations cannot always be the work of an orthopaedic surgeon the usual answer is that an amputation is more often an emergency and that no emergency beds are available in the orthopaedic section. Cannot this be remedied? Amputations should be delegated to a senior surgeon, possibly specialising in amputation surgery if the orthopaedic surgeon is not available. Again speaking from experience, an amputation is frequently left to the end of a list of operations to allow the "major" operations to be carried out first in what may, perhaps, be a long and tiring session. In such cases

it is then that the amputation is apt to be "passed" to a junior. An amputation of a limb commences an entirely new phase of a person's life and should be classed as a major operation. One asks that this may be given due consideration and that emergency beds be allowed in the orthopædic ward.

Before indicating sites of amputation it may be a profitable introduction to summarise the Limb Fitting Service of the Ministry of Pensions. The Minister of Pensions instituted the scheme during the 1914-18 War in order that all Service amputees should be examined by competent limb surgeons. It was to be their duty to specify, order and eventually satisfy themselves as to the supply and satisfactory fitting of the requisite artificial limb for every amputee. After the prosthesis had been supplied the patients were called at regular periodic intervals for inspection of the surgical condition of the stump and of the artificial limb. The necessary repairs were carried out, and, as newly designed limbs were available, the older type of limb was replaced. A record of each attendance was noted, with full details of the condition of the stump, and associated conditions, if any, and registered for detailed examination and future reference. It was proved conclusively that certain lengths of stump were unsatisfactory, and the positioning of scar sites needed more consideration. The type of stump which had given no further trouble to the patient, limb-fitter or surgeon became evident from these records, thus defining the ideal conditions required for each site of amputation.

During the last decade other classes of amputees, including women and children, have been examined under the Ministry's Limb Fitting Service—working in liaison with the Ministry of Labour, the County Councils and Education Authorities throughout the country. Furthermore, the Minister of Health has delegated to the Minister of Pensions the whole work of examining and arranging for the supply of artificial limbs and appliances for every amputee under the National Insurance Act which came into force as from July 5, 1948. It will be seen, therefore, that all amputees in the country are now examined and provided with artificial limbs by the Government under the Limb Fitting Service of the Ministry of Pensions. This will enable their limb surgeons to obtain complete information upon all amputation surgery, to follow up every case and to compile a valuable treatise upon the whole subject.

A scheme has been devised by the Ministry officials whereby the information thus obtained is immediately forwarded to the headquarters of the limb-fitting section for it to be coded and thus facilitate easy and immediate reference to any particular case, or group of cases, regarding a particular problem of amputation surgery and limb supply. It is hoped to make this complete survey and statistical data available to surgeons, and all others interested in rehabilitation work, when sufficient information is available to merit its publication.

No reference has been made in surgical textbooks, or in lectures concerning amputation surgery, with regard to the individual assessment of

disability for any specific amputation. If details of such assessments were known to surgeons it might assist in standardising stump lengths. An inter-departmental committee was set up by the Rt. Hon. J. Griffiths, M.P., and the Rt. Hon. Wilfred Paling, M.P., the Ministers of National Insurance and of Pensions, on March 26, 1946,

“to examine the schedule of assessment of disablement due to specified injuries which is appended to the various war pensions, etc.”

His Honour Judge Ernest Hancock, M.C., was appointed Chairman and the report was published on December 19, 1946, by His Majesty's Stationery Office. The existing war pensions schedule was fully considered and a proposed new schedule—embodying many revised assessments to replace the older schedule—was submitted to the Government. It was adopted. I strongly urge this Hancock Report should be studied by all who have any interest or work in connection with amputation surgery. It would take too much time to make full reference here and now but perhaps that part of the Appendix relating to assessments of the amputations to be discussed this evening will be of some help.

### HANCOCK REPORT—Part of Appendix

#### PART 1. INJURIES ASSESSED AT 20 PER CENT. AND OVER

##### Amputation Cases—Upper Limbs

Description of Injury	Assessment
1. Loss of both hands or amputation at higher site ..	100 per cent.
2. Amputation through shoulder joint .. .. .	90 per cent.
3. Amputation below shoulder with stump less than 8 inches from tip of acromion .. .. .	80 per cent.
4. Amputation from 8 inches from tip of acromion to less than 4½ inches below tip of olecranon .. .. .	70 per cent.
5. From 4½ inches below tip of olecranon .. .. .	60 per cent.
6. Loss of thumb .. .. .	30 per cent.
etc., etc.	(for either arm)

In commenting upon the eight inch stump of the humerus, paragraph 11 of the Report states: “An upper arm stump of less than eight inches, while not sufficient for the fitting of a useful artificial arm, does permit the person to wear a dress arm.” It implies that a longer stump is required without giving any guide as to the optimum length. The truncated humerus must not be too long otherwise the mechanism of the elbow joint in the artificial limb may cause some difficulty in fitting the limb. The ideal length of an upper arm stump is between eight and nine inches as measured from the tip of the acromion. One method of defining the length of the upper arm

# AMPUTATIONS, LIMB FITTING AND ARTIFICIAL LIMBS

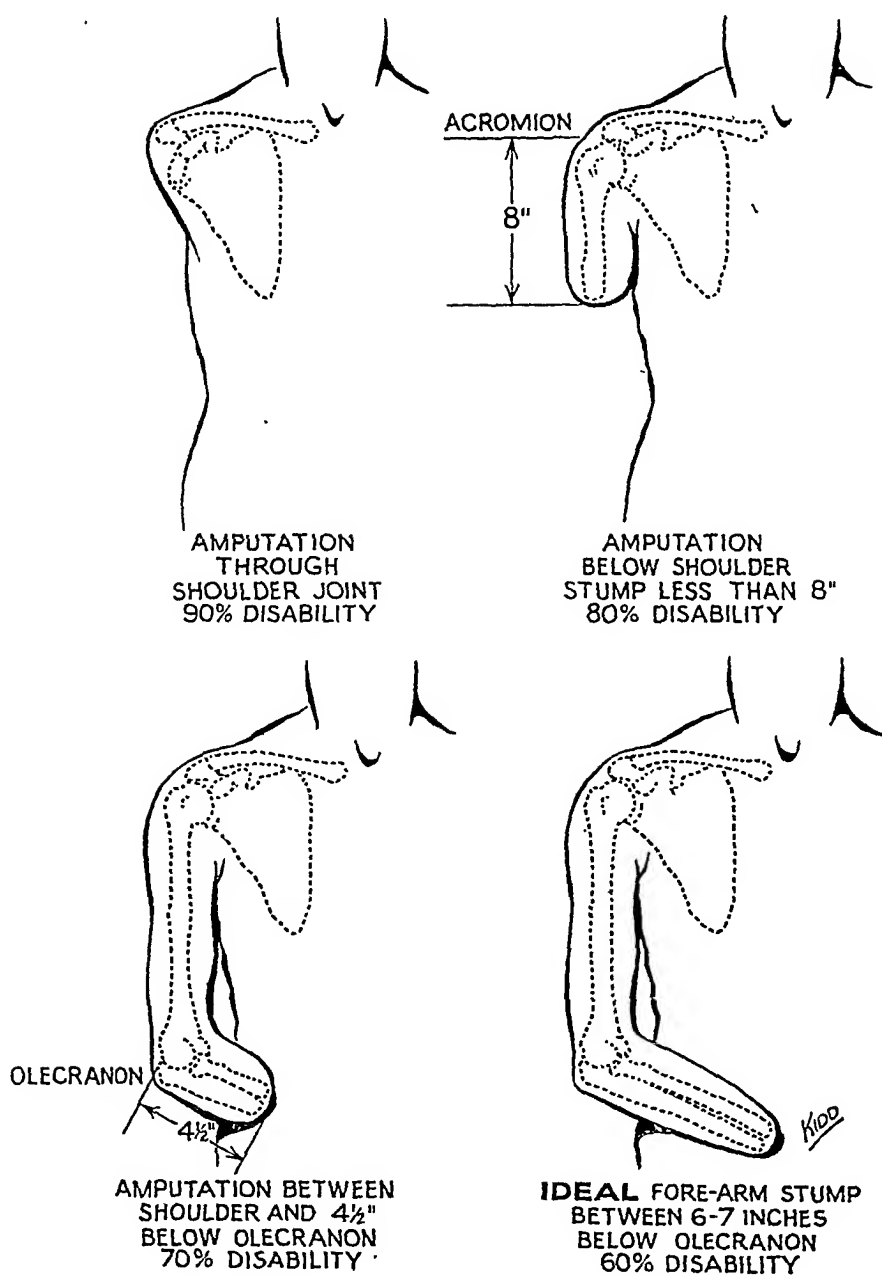


Fig. 1



stump in an adult is at the distal end of the middle third of the bone. The 4½ inch site below the olecranon for a below arm amputation rather indicates another pre-determined site. A useful prosthesis may be fitted in some cases with such a stump, but the ideal length for the forearm stump is 6-7 inches, or again the distal end of the middle third of the ulna.

No mention is made of specific assessments in regard to disarticulation at the elbow or wrist joints but these are included in the schedule at 70 per cent. and 60 per cent., respectively. Experience has proved that an ideal stump is better surgically than a disarticulation and that a more efficient and better controlled prosthesis may be fitted. One further reference is made to the Hancock Report wherein, with one member dissenting, it was agreed that the assessments for a left arm disability should be increased to the corresponding site for the right arm. (Hancock Report, paragraph 10.)

### HANCOCK REPORT—Part of Appendix

#### PART 1. INJURIES ASSESSED AT 20 PER CENT. AND OVER

##### Amputation Cases—Lower Limbs

Description of Injury	Assessment
12. Double amputation through thigh, or through thigh one side and loss of other foot, or double amputation below thigh to 5 inches below knee . . . . .	100 per cent.
13. Double amputation through leg lower than 5 inches below knee . . . . .	100 per cent.
14. Amputation of one leg lower than 5 inches below knee and loss of other foot . . . . .	100 per cent.
15. Amputation of both feet resulting in end-bearing stumps 16-19 —	100 per cent.
20. Amputation through hip-joint . . . . .	90 per cent.
21. Amputation below hip with stump not exceeding 5 inches in length measured from tip of great trochanter . . . . .	80 per cent.
22. Amputation below hip with stump exceeding 5 inches in length measured from tip of great trochanter, but not beyond middle thigh. . . . .	70 per cent.
23. Amputation below middle thigh to 3½ inches below knee	60 per cent.
24. Below knee with stump exceeding 3½ inches but not exceeding 5 inches . . . . .	50 per cent.
25. Below knee stump exceeding 5 inches . . . . .	40 per cent.
26. Amputation of one foot resulting in end-bearing stump	30 per cent.
	(for either leg)

The schedule recognises the loss of both feet as a 100 per cent. disability except that if two end-bearing stumps result the assessment is reduced to 90 per cent.—this no doubt refers to a Syme's amputation of both lower legs. Fig. 2 depicts the sites of assessment as recognised by the Hancock Report, and also the ideal sites of amputation for the thigh and lower leg.

If a very high amputation of the femur is necessary, the assessment will be 80 per cent. whether two inches or five inches are left. If the amputation is made anywhere near the five-inch limit it may cause differences of opinion in measuring the length for assessment purposes, apart from the fact that this length is extremely difficult to fit with an artificial leg of the ordinary socket type, or, the "tilting-table" type of leg. Therefore, rather make the stump longer than the five inches or at least  $1\frac{1}{2}$  inches less. The former will allow the normal socket type of leg to be fitted with comfort and the shorter will allow the "tilting-table" limb to be similarly fitted. A short stump is preferable to a complete disarticulation. Referring to the "middle-thigh" assessment, it is decidedly better for all concerned to leave an ideal length of 10-12 inches. The diagram will show that more of the adductor musculature is retained with the longer ideal stump. It aids the amputee considerably in his control of the prosthesis and prevents abduction of the stump and artificial limb.

If the pathological condition of the leg prevents an ideal length amputation it is suggested that some consultation with a Limb Surgeon may materially assist the patient and his comfort, together with those who will be responsible for prescribing and making the prosthesis eventually to be worn for the remainder of the amputee's life.

The ideal length of the below knee stump is  $4\frac{1}{2}$ -5 inches. There is a diversity of opinion upon the through knee and Syme's amputations; records now being compiled may establish some facts and enable answers to be given later. One may say, however, that the breakdown of "Syme's" stumps which have been seen have usually been on patients who have had some modified type of the true Syme's technique. Both in this and in other countries some excellent Syme's stumps have been seen which have given no trouble to the person after 20 years and more of usage. The type of prosthesis worn is also an important factor in this amputation site.

All details discussed so far relate to amputation sites for adult persons. Child amputees need careful consideration in consequence of the growth of certain bones after amputation. Periodic examinations, X-ray pictures and stump measurements of very many cases, taken over a number of years, confirm the fact that apart from the surgery and subsequent examination of the stump, insufficient attention has been given to the adjustment, repair and replacement of prostheses during the growing years. AND children's crutches require adjustment and replacement: this unfortunately has been somewhat neglected.

It should be remembered that the end of any long bone which appears first in child life is the last to complete ossification and union with the shaft of that bone. The head of the humerus appears before the lower end, and therefore the amputated humerus does grow. When amputating through this bone in a child one should endeavour to leave sufficient for an eight inch stump when growth has ceased. This may necessitate cutting just above the condyles if the amputation is upon a very young

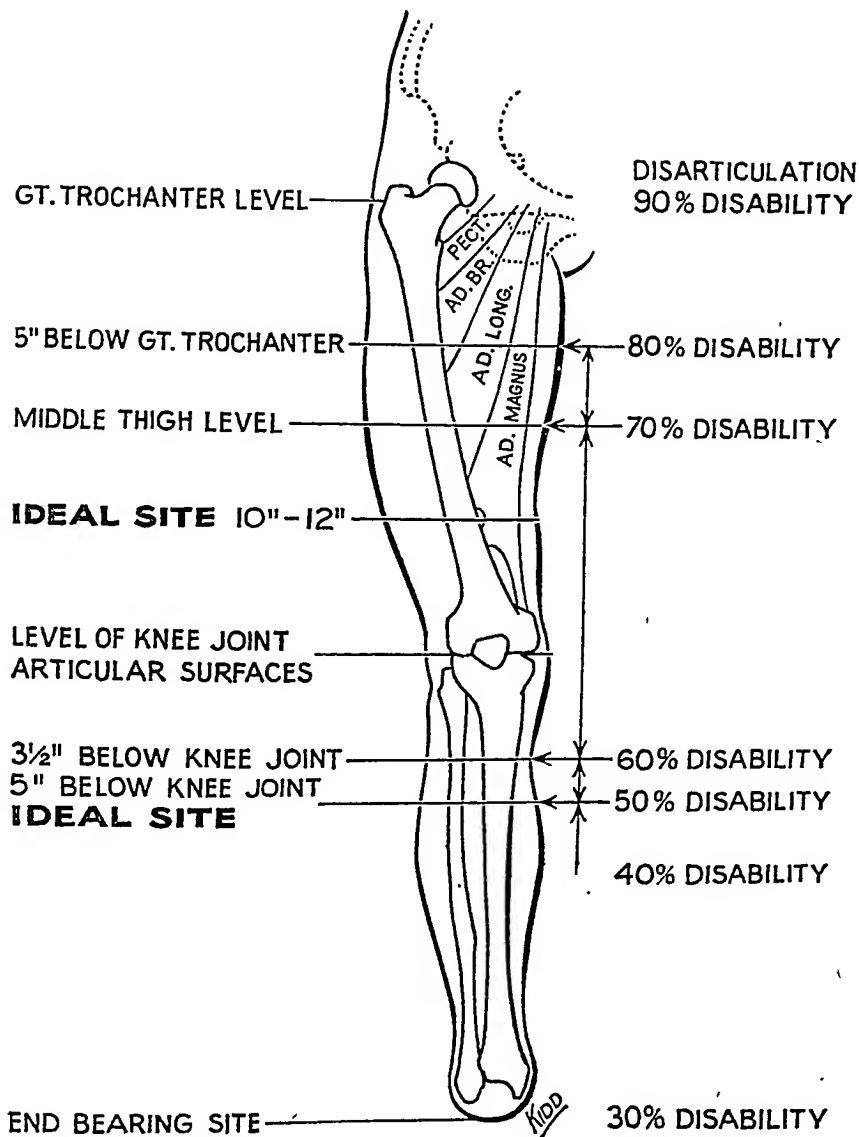


Fig. 2

child. One must be guided by the age of the child when surgery is performed in order to assess where to amputate. The distal ends of the ulna and radius are the last to unite with the shaft of these bones and from this it would appear that the amputated bones in the forearm of a child would not grow. However, children have been seen with the amputated ulna and radius having pushed through the scar at the end of an amputation. Here again one should leave sufficient bone to allow at least a five inch stump when the child is fully grown. The radius must be cut at least half an inch shorter than the ulna, but again one cannot give a definite ruling upon this fact because a child has been seen at the age of 12, after having had an amputation of the forearm at seven years of age and the radius cut shorter than the ulna at the operation, with the radius having pushed its way through the end scar and protruded a quarter of an inch. Many records of child amputees prove that the radius does grow more than the ulna.

The amputated femur of a child does not grow—the growing epiphysis is at the distal end. Many cases have been repeatedly examined and measured with no growth observed. Therefore every endeavour should be made to allow at least eight inches of femur if the ideal length of 10 inches is unobtainable. The site of amputation is naturally governed to a large extent by the cause of the amputation and, again, the age of the child when surgery is carried out. Children have been seen with a disarticulation at the knee joint—through knee amputation—to allow a further period of growth for the femur when an ideal length stump may be obtained by amputation later in life. This re-amputation will naturally take the person away from late school life, an important period in education, or possibly away from the early part of industrial life. It is not only the time required for the surgery, but a considerable time for making, fitting and re-educating the amputee with a new-type limb which makes this procedure problematical. However, the method is worthy of consideration.

The below knee stump of a child needs frequent and regular examination. Both the tibia and the fibula grow after amputation—again dependent upon the age when the surgery is carried out. Several cases amputated at the age of seven have shown the tibia to have grown from half an inch to three quarters of an inch, whilst the fibula has grown more rapidly, and cases have been seen where the end has pushed its way through the scar at the end of the stump. Little growth of these bones is noted after the age of 13 to 14.

The need for regular periodic examination of child amputees cannot be over-emphasised. There is no period when one may say with certainty that a child grows more than at any other time. Children have been seen repeatedly who have required their artificial limbs adjusted on account of growth three and even four times a year about the age of seven and eight, whilst others have required this continued adjustment between 11 and 13 years of age. A three-monthly—even four-monthly—clinic would seem

necessary for all child amputees. The Education Authorities have been responsible for the supply of prostheses before the inception of the National Health Service Act and have in most cases provided each child with duplicate artificial limbs. Every child is now entitled to a duplicate limb which allows one or other of the limbs to be adjusted, repaired or even replaced if the child has grown to such a stage that the original limb cannot be economically repaired. Thus crutches do not have to be used, as was once the case when only one limb was provided for the child. It is important to prevent distortion or tilting of the pelvis by allowing a limb to be worn "short" as the child grows. This is perhaps more important in girls—the question of pelvic distortion may complicate delivery when pregnancy occurs later in married life. Photographic records (actual measurements of neglected cases with X-ray films), have been collected by the Limb Fitting Service and afford conclusive evidence that the child amputee requires the utmost attention during the whole period of adolescence.

The information and statistics now being collected by the Ministry of Pensions prove that there is a poor understanding of the importance of placing any scar in the correct position on an amputation stump. I may arouse some discussion if I say that the majority of cases are not followed up and seen by the operating surgeon AFTER the patient is supplied with the artificial limb. If this follow-up happened more frequently, I feel sure the surgeon would be able to appreciate better where a scar should be placed, both for the comfort of the amputee, and to prevent irritation—often breakdown—of the scar tissue. Operative scars can be placed correctly to lessen the risk of further attention. Traumatic scars cannot be placed where required, but many cases have been seen where a reconstruction has materially assisted the comfort of the amputee and the limb-fitter in making the required limb.

The weight of the body when walking or standing is taken under both feet; when sitting the weight is taken by the two ischial tuberosities. These are the only sites developed by nature to take weight over any long period of the day, and may offer an explanation as to the breakdown of end-bearing stumps, except perhaps the true Syme's when the natural deep tissue under the heel is preserved and used for weight support. A person having lost one leg—either through the hip-joint or through the thigh—will wear a prosthesis which takes the body weight, on the amputated side, under the ischium. But a certain amount of pressure is exerted by the whole of the upper part of the stump in its bearing on the inner surface of the socket of the artificial limb. It is obvious, therefore, that no scars should be placed where they would come into contact with this pressure area.

Speaking first of an amputation through the hip-joint, or one with only two to five inches of femur, a special type of limb is used—a "tilting-table limb." The whole of the buttock area, the front of the lower part of the abdomen and the perineum on the amputated side must necessarily

be in contact with the inner face of the socket of the limb. The body weight is taken by the ischium, but pressure must be exerted over the whole area described above. It is a matter of some difficulty to place a scar which will not have any pressure exerted upon it with this amputation, but the position which appears most suitable is depicted by Figs. 3 and 4, showing the final scar on the lower front part of the abdomen.

The incision is commenced just below Poupart's ligament to allow the femoral vessels to be exposed high up and divided. The nerve should be cut cleanly and nothing further done to it, except, perhaps, that the accompanying nutrient artery may require to be tied. Amputated nerves should NOT be treated in any manner whatever. Fig. 4 shows an ideal stump or shape for this site of amputation, with the short femur flexed to the "sitting" position. It closely conforms to the shape of the natural pelvis and is more satisfactory to all concerned than a complete disarticulation of the femur. Many cases with such short amputations have been seen with a large amount of muscular and fatty tissue left in a pendulous mass somewhat like a through femur amputation, but without any bone in the "mass." This excess of tissue is very uncomfortable to the patient and should be avoided.

When the surgery of the tissues and the bone of this, and in fact all amputations, is completed, the skin flaps should be placed in their final position and a few sutures inserted to assess the final position and shape of the scar. If this final scar does not appear to be a clean linear one, here is the opportunity to refashion the truncated musculature, the skin flaps, or possibly both, to produce a clean, linear, non-puckered scar without any infolded edges of the skin flaps or "dog-ears." Intertrigo follows infolded scars and is often difficult to treat, apart from having to "leave off" the artificial limb during treatment with loss of time and employment. I cannot avoid stressing this matter of what appears to be hurried suturing and closing of amputation surgery, and hope that this seemingly small appeal may be given the attention it requires.

Fig. 5 illustrates the need for a posterior scar on an ideal above knee stump; a similar sketch would show the same "mechanical" reason for a correctly placed posterior scar on an ideal below knee stump. Both stumps propel the socket section of the artificial limb forward in walking. The diagram shows the stump pushing or swinging forward the artificial limb with the scar quite free from the posterior surface of the socket. The leg having been brought forward, it is then kept in extension by the heel being pushed on the floor and the stump pressing backwards on the posterior inner surface of the socket—with the scar again quite free from pressure. In standing, the scar is still free. Of course the scar must not be placed high on the posterior surface but posteriorly on the end of the stump as indicated. Some guide may be given in describing the length of the anterior flap as approximately equal to the diameter of the stump itself for all posterior scars. All leg stumps rise and fall in the limb socket, producing what is termed "piston action." End scars, formed from

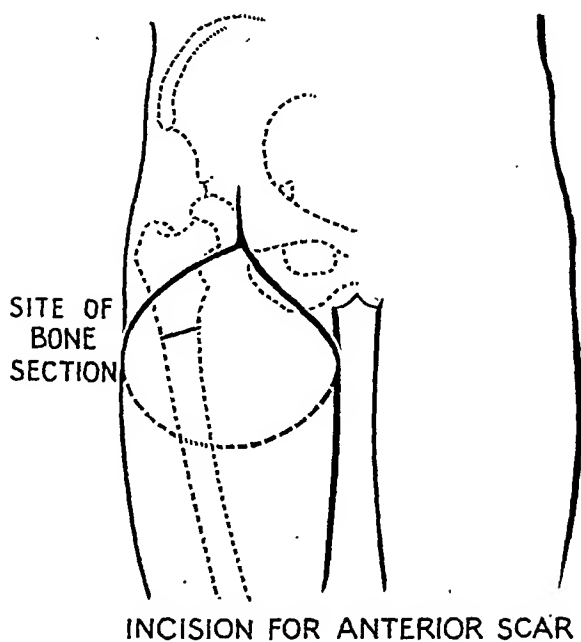


Fig. 3. Short femur amputation—Incision for anterior scar.

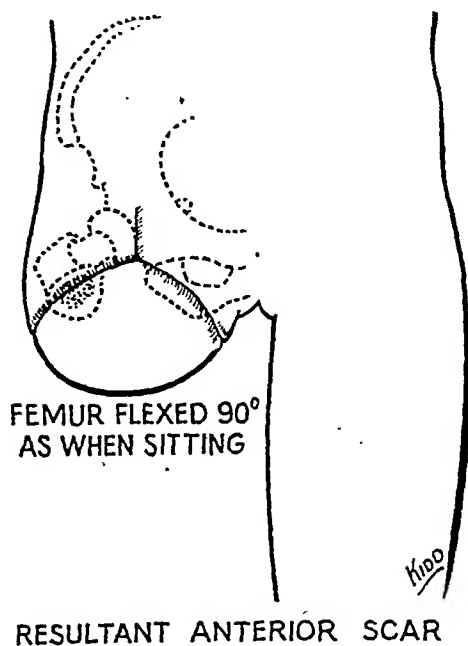


Fig. 4. Short femur amputation—Resultant anterior scar.

equal skin flaps, tend to become adherent to the bone end and this piston action pulls the scar over the bone end with consequent irritation and often breakdown. A full thickness flap tends to avoid such troubles from piston action.

Figure No. 2 illustrates the ideal above knee site. One should preserve as much of the adductor musculature as possible and aim at making the truncated femur 10-12 inches to include most of the adductors except the lower part of the Ad. Magnus. The extra length over the eight inch-stump referred to in the Hancock Report is of extreme value and assists in prevention of abduction of the thigh stump—and the artificial leg—which is so often seen with shorter stumps. The musculature should be fashioned to give a tapering stump without excess of tissue. Cut the nerve a little above the ends of the muscles and preserve complete hæmostasis ; as with all amputations. Some surgeons advocate suturing the cut ends of the musculature over the end of the stump with mattress sutures. I have seen above knee stumps where the whole lower end of the stump rotates when the thigh musculature is activated or contracted. This rotation is a source of trouble and produces a chafing of the skin with an ordinary limb. With ordinary trimming of the musculature and a linear scar it does not appear that this end suturing is required. The above knee stump does not require to be more than 10-12 inches as previously taught ; greater length does not give better or more control, but produces circulatory troubles.

The ideal below knee stump should be 4½-5 inches with a posterior scar. Again a longer stump does not assist in controlling a limb but certainly produces breakdown from circulatory trouble, as has been seen repeatedly with long below knee stumps. Stumps measuring only 1½ inches below the knee can, and have been, satisfactorily fitted, but one is

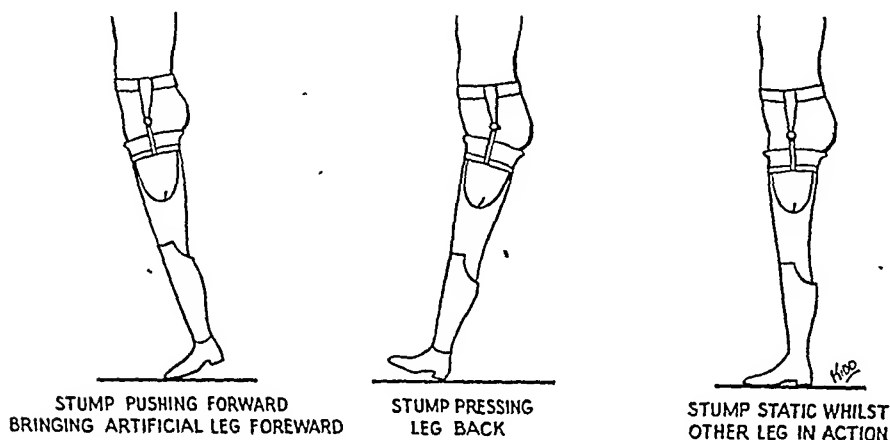


Fig. 5. Posterior scar always free from contact with socket.



asked to keep to the ideal length. If it is at all possible the knee joint should be preserved rather than a through knee amputation. The fibula tends to grow after amputation in an adult. It should be cut half an inch shorter than the tibia and the front edges of both bones should be bevelled off, with the sawn ends filed smooth and round, to prevent the full thickness skin flap being damaged by the piston action of the stump in the socket when the limb is used. DO NOT remove the fibula unless it is so severely traumatised to render it necessary. The exposure of the articular surface of the fibula on the head of the tibia allows some pressure to be imparted to the site and causes pain to the patient when the limb is worn. Many cases prove this contention.

The Syme's amputation appears from records to be quite serviceable. It is the "modified" Syme's amputation which appears to have only a life of about seven to eight years when they break down and then an ideal below knee re-amputation is usually performed. An important factor with the Syme's is that a person can walk on the end of the stump in an emergency. The original Syme's technique appears quite satisfactory both in this and other countries. It is still used extensively in the U.S.A. and in Canada with good results.

Dealing with the upper limb one asks that the disarticulation of the shoulder joint should be avoided if possible. The head of the humerus, however short, should be left both for the comfort of the patient, with and without limb wearing, and to allow a prosthesis to be fitted which will certainly be of more value than the type supplied for a disarticulation site. The ideal length of the amputated humerus is eight to nine inches as measured from the tip of the acromion. Shorter stumps can be fitted with an efficient prosthesis. If there is only an inch of humerus below the anterior axillary border one can use an artificial arm if the patient has the will to master its control. The equal flap method has been advocated for arm amputations—even the guillotine—to be followed by later surgery. It is said that there is no piston action of the arm stump in the socket. This is not correct. There is not so much piston action as with the leg stump, but various controls of the actions of the artificial arm depend upon voluntary piston action. It is, therefore, quite reasonable to ask for a posteriorly situated scar on the above elbow stump, with tapering musculature, clean division of the nerves above the end of the musculature, complete hæmostasis and a linear non-puckered scar without dog-ears.

An ideal forearm stump should be between 6-7 inches and again the question of scar positioning is very important. A terminal scar has been asked for but results are showing that this end scar, becoming adherent to the amputated ends of the ulna and radius, is upset by the remaining pronation of the amputated forearm. In addition, the pulling effect of the scar over the bone ends, during piston action imparted to the stump in the socket whilst using various mechanical appliances, again causes irritation and breakdown of the terminal scar. A full thickness flap can be designed with the scar placed on the dorsal surface of the forearm.

Mutilation of the hand requires the most skilled attention, as will be detailed in a special lecture. Assessments for the various disabilities arising from mutilated and partially mutilated hands are referred to in the Hancock Report.

An all-important period connected with the surgery of an amputation is that immediately after the operation. Too many patients are sent back to bed, made comfortable and left until "the stitches are taken out." The above knee and the below knee stump should be kept in extension for the first two days to prevent flexion, after which active movement of the joint above the amputation site should be carried out with an increase of the range of movement upon each succeeding day. When the stitches are removed there should be full range of movement of the joint without any discomfort to the patient. It is disconcerting to see the number of above elbow amputees who cannot raise the stump above the level of the shoulder because these exercises have not been carried out.

The next stage in preparation for limb wearing is to reduce the œdema. Plaster pylons have been used for above knee stumps but the peculiar abduction gait acquired from the use of the pylon remains for a considerable time after the correct limb has been used. A pylon can only be used a few hours each day. A more widely used method is that of using crêpe bandages. Each site of amputation requires the correct width of bandage to be used. An above knee stump requires a long six or eight inch bandage (probably two, even three sewn end to end), the below knee requires a four inch and the arm stumps require four or three inch bandages, dependent upon the size of the stump. Above knee stumps have often been seen having had a four inch bandage used. It is harmful and worse than using no bandage at all.

Fig. 7 illustrates how the bandage is applied to an ideal above knee stump. All amputees should be instructed how to apply their own bandages, and to re-apply them several times a day, except the above knee application which will require a second person to do this. Furthermore, bandages should be used for at least six months after the artificial limb is first used. Fig. 6 shows a method of exercising the above knee stump, either in the hospital, or at home, making use of an ordinary chair, some heavy string and a weight.

Massage is NOT required for any amputation stump. Any uneven pressure or interference with the musculature of the stump, especially near the nerve endings, can and does irritate the neuromatous growth of the nerve end, and unfortunately has the effect of stimulating the "phantom leg."

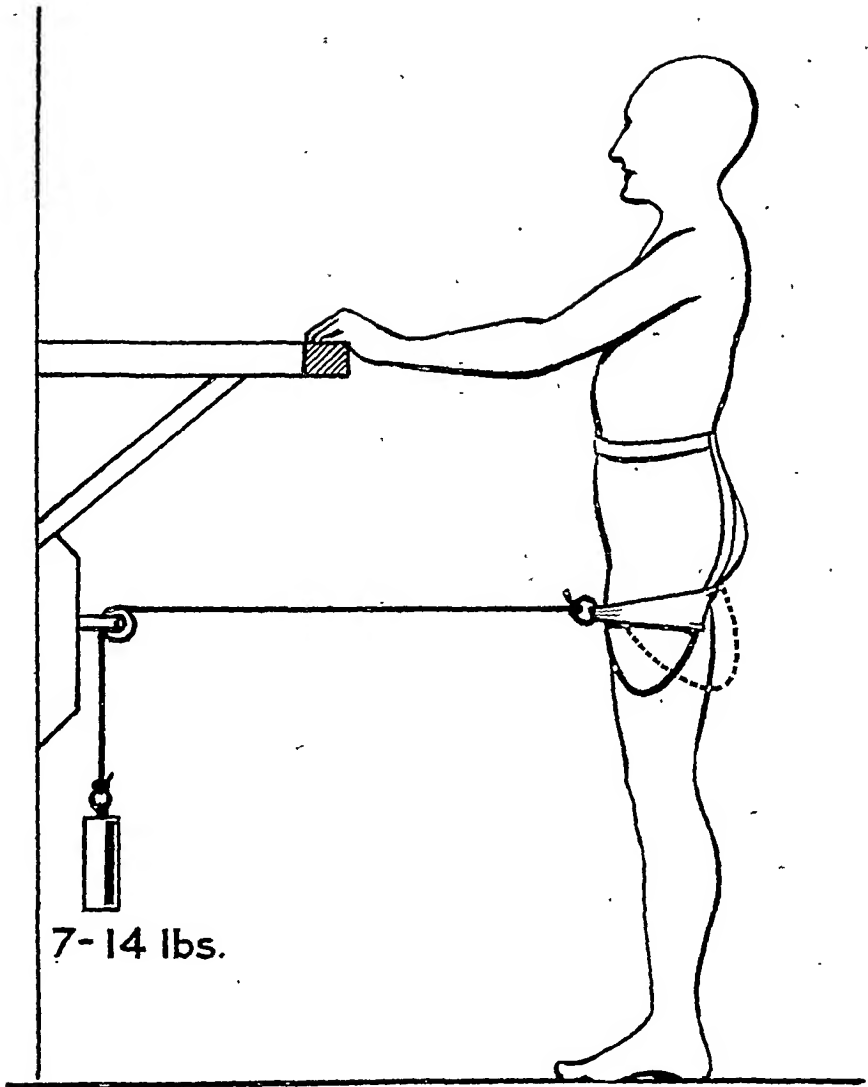


Fig. 6A. Exercising an above knee stump.

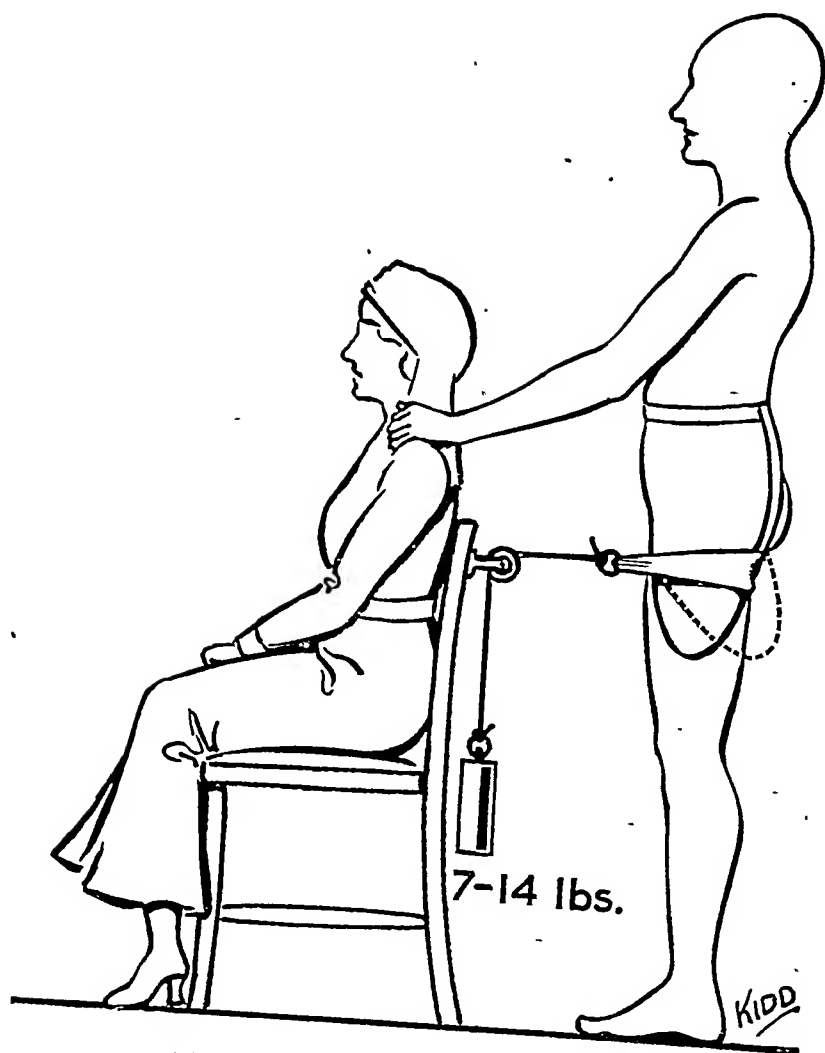


Fig. 6B. Exercising an above knee stump.

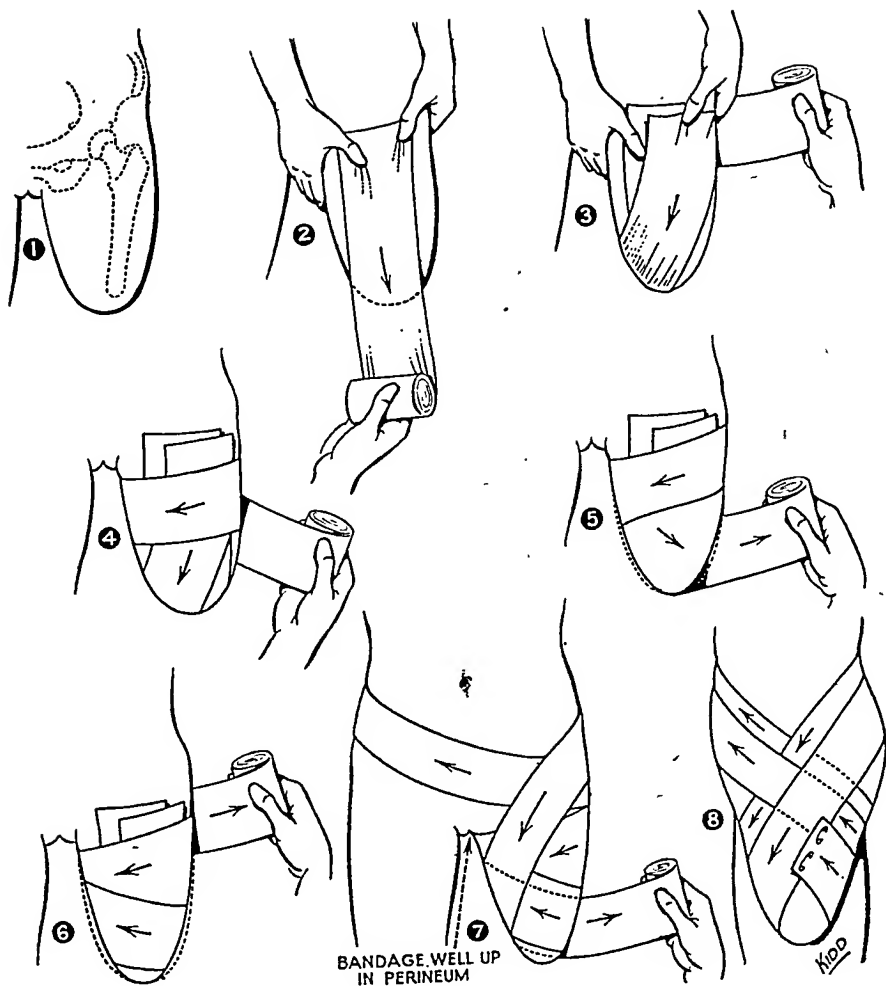


Fig. 7. Method of bandaging an above knee stump.

# SUMMARY

It is suggested that all amputations should be treated as major operations and carried out in the orthopædic wards where a quota of beds, including emergency beds, should be designated for this work.

It is recommended that the Hancock Report, published by H.M. Stationery Office, December, 1946, defining the assessment of disability arising from each site of amputation should be made known to, and consulted by, surgeons.

Records and coded statistics compiled during the past 30 years by the Ministry of Pensions prove conclusively that there is an ideal length of stump, a correct position for the operative scar, the necessity for the non-treatment of severed nerves, and routine post-operative treatment for each type of amputation.

The child amputee should be re-examined frequently each year in regard to stump condition, growth of the stump, adjustment, repair and possible replacement of the prosthesis worn.

Crêpe bandaging and the exercise of all joints above the amputation and the musculature of the stump itself are necessary to expedite limb-fitting.

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A demonstration of a range of normal artificial limbs was given after the lecture, together with some illustrations of the control of the limbs by several amputees. The suction socket above knee limb was described, and one patient who had worn the limb satisfactorily for some time showed how it was "put on" and successfully used.

## THE PORTRAITURE OF WILLIAM HARVEY

THIS MONTH, THE office of the *Annals of the Royal College of Surgeons of England* will issue its first independent publication. This is the Thomas Vicary Lecture, entitled *The Portraiture of William Harvey*, delivered at the College by Mr. Geoffrey Keynes, F.R.C.S., on November 17, 1948.

In this Lecture Mr. Keynes gives a brief account of the history of portraiture in Great Britain, and then examines in detail the problems of the portraiture of William Harvey, a subject which has remained until the present time in a state of confusion and uncertainty. The credentials of between 30 and 40 pictures are examined so as to determine the few which may be regarded as having been painted from the life; contemporary engravings and etchings and the fine bust by Edward Marshall in the Harvey Chapel at Hempstead, in Essex, are also considered. The important picture in the Hunterian Collection at Glasgow is now described for the first time, and also, in an addendum to the Lecture, a newly identified portrait of Harvey at the age of 45.

Following the text of the Lecture is a full *catalogue raisonnée* of all the representations of Harvey, both actual and reputed.

The Lecture when delivered was fully illustrated with lantern slides, and the majority of these have been reproduced in collotype.

The volume is a small quarto of 42 pages with a frontispiece of Harvey's head from the portrait at the Royal College of Physicians and 32 other plates. It is bound in blue cloth lettered along the back.

The book is published at 25s. net, and may be obtained from the office of the *Annals* or through the booksellers. Part of the edition is being made available to American buyers through Henry Schumann Inc., Publishers, 20 East 70th Street, New York, 21.

## CARDIO-VASCULAR ANOMALIES

THE BOMB DESTRUCTION to the College Museum destroyed the whole of the valuable Peacock Collection of Anomalous Hearts, as well as those dissected and studied by Sir Arthur Keith. Altogether only 36 of the original 130 specimens remain intact. Thirty-five of the originals were those upon which Peacock based his treatise "Malformation of the Human Heart" published in 1858; seven of these survived the disaster of May 10th-11th, 1941.

Apart from the Maude Abbott Collection in Montreal there is now no collection of these important conditions in sufficient numbers to permit detailed study.

A research unit has begun work on a Collection for the College Museum. Considerable progress has been made. Reorganization and re-classification studies are well in hand and actual experimental work on problems concerned with the surgery of the Anomalous Heart and Vessels is about to commence.

These lesions are not very common, so that accumulation of a large representative Collection depends for its success upon individual donors' generosity and thoughtfulness. The common benefit deriving from such a collection of material is too obvious to need emphasis, especially in these times when Cardiac Surgery is rapidly gaining a place of respect.

The common purpose may also be served by individual collectors making known to this research unit the location and contents of their collections. With this information it is possible for a worker engaged on a given problem, rapidly to locate material for study. At the same time the collector's devotion to surgery will be utilized to the full. Many unique and rare examples must at present be hidden on their owner's shelves. The purpose of a collection should be to leave the next generation with a basis of fundamental material upon which to build their surgery; this purpose is only served if the collection is made available to that generation.

Contributions of specimens will be greatly appreciated by Professor Andreassen, who is at present working on the new collection at the College.

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### FORTHCOMING LECTURES AND DEMONSTRATIONS FOR 1950.

3rd January, at 5.0 p.m.	..	..	..	Erasmus Wilson Demonstration by C. E. Shattock.
6th January, at 5.0 p.m.	..	..	..	Erasmus Wilson Demonstration by C. E. Shattock.
10th January, at 5.0 p.m.	..	..	..	Erasmus Wilson Demonstration by Philip H. Mitchiner.
11th January, at 5.0 p.m.	..	..	..	Erasmus Wilson Demonstration by L. W. Proger.



17th January, at 5.0 p.m.	.. .. .	Arris and Gale Lecture
“The Diagnosis and Management of Hirschsprung’s Disease”	.. .. .	by F. D. Stephens.
18th January, at 5.0 p.m.	.. .. .	Arris and Gale Lecture
“Surgical Aspects of Renal Damage in Childhood : Assessment, Salvage and Aftermath”	.. .. .	by D. F. E. Nash.
20th January, at 5.0 p.m.	.. .. .	Erasmus Wilson Demonstration
		by Philip H. Mitchiner.
24th January, at 5.0 p.m.	.. .. .	Erasmus Wilson Demonstration
		by L. W. Proger.
9th February, at 5.0 p.m.	.. .. .	Hunterian Lecture
“Congenital Deformities of the Urethra, Vagina and Anus”	.. .. .	by Denis J. Browne.
16th February, at 5.0 p.m.	.. .. .	Hunterian Lecture
“A Review of 500 surgically treated cases of Lumbar Intervertebral Disc Protrusion, with especial reference to the late results of operation”	.. .. .	by J. E. A. O’Connell.
21st February, at 5.0 p.m.	.. .. .	Hunterian Lecture
“Factors contributing to safety in Surgery of the Thyroid”	.. .. .	by J. E. Piercy.
23rd February, at 5.0 p.m.	.. .. .	Hunterian Lecture
“Malignant Disease of Thyroid Gland”	.. .. .	by H. L. M. Roualle.
28th February, at 5.0 p.m.	.. .. .	Hunterian Lecture
“Fractures of the Radius and Ulna”	.. .. .	by E. M. Evans.
7th March, at 5.0 p.m.	.. .. .	Hunterian Lecture
“Post-operative Venous Thrombosis and Embolism”	.. .. .	by R. S. Murley.
9th March, at 5.0 p.m.	.. .. .	Hunterian Lecture
“Renal Denervation”	.. .. .	by J. B. Oldham.
14th March, at 5.0 p.m.	.. .. .	Hunterian Lecture
“Villous Tumours of the Rectum”	.. .. .	by M. R. Ewing.
16th March, at 5.0 p.m.	.. .. .	Hunterian Lecture
“The Respiratory Responses to Operative Trauma”	.. .. .	by E. M. Nanson.
11th May, at 5.0 p.m.	.. .. .	Hunterian Lecture
“Ruptures of the Rotator Cuff”	.. .. .	by H. F. Moseley.
15th June, at 5.0 p.m.	.. .. .	Hunterian Lecture
“Cutaneous Cancer in relation to Occupation”	.. .. .	by S. A. Henry.

# DIARY FOR OCTOBER

Fri. 21	10.00	DR. H. L. MARRIOTT—Fluid Balance.
	11.15	DR. H. L. MARRIOTT—Fluid Balance.
	5.00	DR. W. W. MUSHIN—Local Analgesia.
	5.00	PROF. PEDRO BELOU—Synthesis of the Anatomical Investigations realised over a period of 33 years on the Morphology of the Human Arterial System.
Mon. 24	10.00	DR. W. W. MUSHIN—Local Analgesia.
	11.15	DR. W. W. MUSHIN—Cyclopropane and Absorption Technique.
	5.00	DR. W. W. MUSHIN—Cyclopropane and Absorption Technique.
	5.00	PROF. PEDRO BELOU—Results obtained from Cinematography in Colour for the Objective Interpretation of the Morphology of the Human Arterial System.
Tues. 25	10.00	DR. C. A. KEELE—Pharmacology.
	11.15	DR. C. A. KEELE—Pharmacology.
	5.00	DR. A. H. GALLEY—Caudal Analgesia.
	5.00	MR. E. S. R. HUGHES—Arris and Gale Lecture—Development of the Mammary Gland.
Wed. 26	10.00	DR. C. J. MASSEY DAWKINS—Epidural and Posterior Splanchnic Block.
	11.15	DR. T. CECIL GRAY—Relaxant Drugs.
	5.00	DR. T. CECIL GRAY—Relaxant Drugs.
Thur. 27	10.00	DR. FRANCIS T. EVANS—Anæsthesia for Perineal Surgery.
	11.15	DR. I. W. MAGILL—Intubation.
	5.00	DR. E. H. RINK—Anæsthesia for Cardiac Surgery.
	5.00	MR. A. E. W. McLACHLAN—Bone Syphilis.
Fri. 28	10.00	DR. W. S. McCONNELL—Nitrous Oxide and Vinesthene for Dental Surgery.
	11.15	DR. A. I. PARRY BROWN—Anæsthesia for Thoracic Surgery.
	5.00	DR. A. I. PARRY BROWN—Anæsthesia for Thoracic Surgery.
Mon. 31	10.00	PROF. SPURRELL—Anoxia.
	11.15	PROF. MACINTOSH—Volatile Anæsthetics.
	5.00	PROF. MACINTOSH—Volatile Anæsthetics.

A series of Tutorials in Anæsthetics will also be held during the same period as the Lectures (October 17th-November 4th), and will consist of 10 one-hourly periods, commencing at 6.15 p.m.

# THE ÆTIOLOGY, PATHOLOGY, DIAGNOSIS AND TREATMENT OF ACUTE PANCREATITIS

## A Review of 110 Cases

Hunterian Lecture delivered at the Royal College of Surgeons of England  
on  
28th February, 1949

by  
R. A. Russell Taylor, F.R.C.S., M.R.C.O.G.

Medical Superintendent and Surgeon, Pinderfields General Hospital

IN THE PREPARATION of this lecture, only cases which were proved (1) at operation, (2) at post mortem, or (3) clinically, with a raised urinary diastase or serum amylase have been included.

In order to appreciate thoroughly the difficulties which face the surgeon in the diagnosis and treatment of acute pancreatitis, it is essential to give a résumé of the ætiology and pathology of this still obscure condition.

### ÆTIOLOGY

Until recently, very few observations on definite cases of acute pancreatitis regarding the anatomical variations in the arrangements of the common bile duct and the pancreatic ducts, had been made.

Popper *et al.* (1948) state that there is a common channel in 89 per cent. of cases of pancreatic œdema, acute pancreatitis and pancreatic necrosis. Howard and Jones (1947) found that where there was an obstruction at the Ampulla of Vater, fluid injected into the common bile duct refluxed into the duct of Wirsung in 54 per cent. of specimens, and in cases where the duct of Santorini was present, the incidence of reflux rose to 82 per cent. It is therefore justifiable to suggest that, other things being equal, there might be a greater incidence of acute pancreatitis in patients with a patent duct of Santorini, and I commend this fact to you for further investigation. To pursue this point further, it is also reasonable to assume that when there is an obstruction at the Ampulla of Vater, the pressure in the pancreatic ducts is less than that in the biliary passages when there is a patent duct of Santorini, thus allowing a reflux of bile along the duct of Wirsung. That this is not the whole story is evident from the fact that cases of acute pancreatitis have also been described in which the ducts have opened separately into the duodenum and rare cases in which the necrosis has been restricted to the region drained by the duct of Santorini.

In 50 per cent. of cases, it is said that the obstruction is caused by a gall-stone, but in less than 5 per cent. of cases is this stone found, as it may have been passed into the intestine after producing œdema or necrosis of the pancreas. Other causes of obstruction may be pancreatic calculi, round worms, tumours of the head of the pancreas, aneurysm of the neighbouring vessels, and in a case described by Forty (1939) a barley corn.

Obstruction which would allow reflux of bile along the pancreatic duct may also be produced by spasm of the sphincter of Oddi; the spasm being

usually secondary to acute gastro-duodenitis which itself might be secondary to acute corrosive poisoning or occur reflexly in the same way as pylorospasm in cases of acute cholecystitis.

In a large number of cases there is a marked proliferative metaplasia of the pancreatic duct epithelium, which causes a certain degree of obstruction and stagnation of bile and pancreatic juice with a subsequent rise of pressure and activation of the trypsinogen in the intraductal system.

Acute hæmorrhagic pancreatitis has also been produced by injecting a large number of irritating fluids (not bland substances) into the pancreatic duct, but it was pointed out by Rich and Duff (1936) that the typical lesion is not produced unless the amount of fluid injected is sufficient to rupture the pancreatic acini and they conclude that the escape of trypsin into the interstitial tissues is the essential causative factor.

Pure bile appears to be incapable of activating trypsinogen to trypsin, but it has been shown that enterokinase in the mucosa of the gall-bladder and bile infected by bacteria and cell debris can do so. If infected bile is forced along the duct of Wirsung, the bile salts will activate the pancreatic zymogen and there is digestion of the tissues which produces œdema, necrosis and hæmorrhage.

Popper *et al.* (1948) attempted to transform pancreatic œdema into pancreatic necrosis by the following methods, but all with negative results :—

- (1) Ligature of the cisterna chyli in order to block the lymphatic drainage from the pancreas.
- (2) Temporary clamping of the portal vein.
- (3) Shock produced by trypsin.
- (4) Gross trauma.

They also showed that temporary occlusion of the gastro-duodenal artery applied for 30-40 minutes in a day, did not cause any marked microscopic changes in the pancreas, but that the same experiment performed on an animal with pancreatic œdema led to the development of pancreatitis, the extent of which was determined by the previous degree of œdema. In cases of low-grade œdema, only fat necrosis developed, but in cases with extensive œdema, all the pathological changes of acute pancreatitis were present. Wightman (1948) pointed out that the amount of damage produced in pancreatitis depended upon (1) the volume of fluid which had diffused into the connective tissues of the gland, (2) the concentration of the enzymes in the juice, and (3) the number of large blood-vessels with which it came in contact.

The pancreas may also be infected from distant foci by the blood stream as is well illustrated in cases suffering from infective endocarditis, cholecystitis, ulcerative colitis, appendicitis and pyæmia. Pancreatic abscesses may result from retrograde thrombosis and suppurative pyelophlebitis.

Acute pancreatitis may also be observed as a complication of influenza, typhoid fever, smallpox and mumps, but in the latter cases, suppuration

or necrosis never occur. Very rarely it has been attributed to tuberculosis and syphilis.

Paxton and Payne (1948) found that 18 per cent. of their cases were admitted to hospital in an intoxicated condition and that in 25 per cent. of cases the pain came on immediately after a heavy meal. Cole (1938) however, found that the interval between a meal and the onset of pain was usually 2-3 hours.

Cases of acute pancreatitis have followed penetrating and non-penetrating abdominal injuries and also operations on the stomach, duodenum or lower end of the common bile duct when the pancreas has been injured.

Ackerman (1942) reported on a case of acute pancreatitis which followed transfusion with incompatible blood, which at autopsy showed thrombosis of the pancreatic veins.

The frequent association of acute pancreatitis with infection of the biliary tract suggests that the lymphatic route is a possible connexion between the inflamed gall-bladder and the pancreas, but the experiments of Kaufmann (1927) on rabbits practically discounted this.

### PATHOLOGY

Acute pancreatitis occurs most commonly about 40-60 years of age and with about equal frequency in the two sexes. There also seems to be a definite association with obesity, cholecystitis and cholelithiasis.

Pratt (1940) maintains that acute pancreatitis is not an infection but an intoxication by the pancreatic ferments. Nevertheless, the intensity of the primary destructive changes determines the extent of the pathological changes because this condition of auto-digestion may be self-perpetuating and progressive even although the original stimulus has been removed. The progress of the disease may be continuous or intermittent and it may become arrested at any stage.

### Appearances at Post Mortem

The body is sometimes very obese and in approximately 50 per cent. of cases the patient is overweight. There may be local discoloration of the abdominal wall around the umbilicus (Cullen's sign) and in the loins (Grey Turner's sign). This discoloration is only seen in severe cases where the patient has lived for 2-3 days after the acute onset, and must not be confused with post-mortem staining.

On opening the abdomen it must be remembered that acute necrosis may be present and yet macroscopically the pancreas may appear normal. The mildest type of acute pancreatitis is that known clinically as "transient pancreatitis" and recovery is common. Here we get œdema of the pancreas in which the intrapancreatic and peripancreatic œdema consists of pancreatic fluid which has escaped into the pancreatic interstitial tissues. This œdema does little or no harm and will disappear soon after the secretory stimulus has been discontinued. It is usually accompanied by catarrhal changes in the duodenum which extends up the pancreatic duct. The pancreas itself may be enlarged to 2-3 times its normal size and is of

varying consistence. It is indurated and small areas of fat necrosis may be present, but hæmorrhage is slight or absent. The changes may involve the whole organ or be localised to the head, body or tail, the usual percentage being, whole of pancreas, 73.1 per cent., body, 19.2 per cent. and tail, 7.7 per cent. (Fallis, 1939). The retroperitoneal tissues are also usually œdematous or infiltrated with blood.

The next stage, that of hæmorrhagic pancreatitis, is seen if the arterial blood supply has been interrupted. The resistance of the acinar and interstitial cells has been weakened by this temporary ischæmia and they are attacked by the enzymatic action of the œdematous fluid in which the trypsinogen has been activated to trypsin by the bacteria and cellular debris.

In the most severe cases, the pancreas is seen as a large, dark, purplish, soft and friable mass on the posterior abdominal wall, shining through the peritoneum of the lesser sac. The peritoneal cavity may contain sanguinous or sero-sanguinous fluid which is present in the greatest amount in the lesser sac. This fluid may, however, have a yellowish-green colour due to bile staining. It is invariably sterile, but later it may become infected, resulting in a localised or generalised peritonitis.

Gangrenous pancreatitis is generally regarded as a late stage of hæmorrhagic pancreatitis and therefore occurs in cases which have survived the initial stages. The pancreas becomes softened, breaking up of the tissues with subsequent infection occurs, and a local or general peritonitis results.

In suppurative pancreatitis there may be a considerable destruction of the gland due to (1) one or more abscesses in the pancreas itself, (2) retroperitoneal abscess, or (3) an abscess in the lesser sac. The infection may spread along the pancreatic ducts or directly from contact with the infected pancreatic tissues. The abscesses are usually sterile and contain thin pus or watery turbid fluid. Grey sloughs of pancreatic tissue or necrotic fatty tissue may also be present and the necrotic tissue may subsequently liquefy and give rise to pseudocysts of the pancreas.

In patients who survive, fibrosis occurs, which, if extensive, results in a reduction of the glandular tissue, distortion of the ducts and the formation of pancreatic cysts, i.e., a similar picture to that found in cases of chronic pancreatitis.

In addition to the above, other pathological conditions are usually present :—

TABLE 1

Associated Pathology	Lewison (1940)	Fallis & Plain (1939)
Chronic Cholecystitis .. ..	70%	57.7%
Acute Cholecystitis .. ..	2%	15.4%
Acute Cholelithiasis .. ..	80%	80%
Choledocholithiasis .. ..	9%	8%
Ampullary Stones .. ..	3%	—
Normal Gall-Bladder .. ..	20%	26.9%

In these cases the gall-stones are invariably small and the bile is usually infected, dark in colour and may be blood-stained.

### Microscopic Appearances

Three main pictures may be seen. In the first, the pancreas is seen to be uniformly hæmorrhagic; secondly there is marked necrosis of the glandular and interstitial tissues with a varying amount of hæmorrhage around the necrotic areas and in the areolar tissues, and thirdly, the pancreas is mainly necrotic.

When hæmorrhage is the outstanding feature, the whole glandular tissue is infiltrated with blood. The activated enzymes digest the blood-vessel walls, and the severity of the secondary hæmorrhage, in and around the pancreas, depends to a certain extent on the size of the blood-vessels involved. Marked thrombosis of the blood-vessels, which have hyaline degenerative changes in their walls, can also be seen.

Diffuse necrosis of acini may occur or the necrosis may affect the glandular and interstitial tissue with accompanying leucocytic infiltration. It is interesting to note that the inflammatory reaction is greatest in the less acute cases. The appearance of the parenchyma and the hæmorrhage strongly suggests that the condition is due to some toxic agent, but, although bacteria, e.g., *B. Coli* and *Streptococci* have been found, in some cases in large numbers, there is not enough evidence to support the theory that this condition is the result of bacterial invasion.

It must not be forgotten, however, that hæmorrhage into the pancreas may also occur in blood diseases, sepsis and poisoning, especially in fat people.

### Fat Necrosis

This is the most distinctive feature of acute pancreatitis, and is seen as dull opaque, yellowish-white areas suggestive of drops of tallow, but they are not raised above the surface. Their size varies from that of a pin-head to about  $\frac{1}{4}$ -inch in diameter and they are most abundant in the vicinity of the pancreas, but the retroperitoneal tissues, omentum, mesentery, mediastinum, pericardium, pleura and anterior abdominal wall, may also be involved. It is invariably attributed to the action of lipase following its liberation due to damage to the gland tissue by infection, abscess formation or mechanical injury. The lipase has travelled along the lymphatics or by the blood stream and this theory explains its patchy nature and also the occurrence of distant foci in the bone marrow, etc. Pancreatic lipase splits up the fatty molecule into glycerine and fatty acid and the latter combines with calcium to form an insoluble soap. If the patient survives, these deposits are absorbed in a matter of weeks.

Microscopically the necrosed fat cells are seen to be wholly or partly opaque and the whole area is surrounded by a ring of leucocytes.

Fat necrosis is not, however, pathognomonic of acute pancreatitis as it may occur with perforation of an ulcer of the second part of the duodenum.

Also it is necessary to distinguish between fat necrosis in acute pancreatitis and post-mortem fat necrosis. In the latter condition, only scattered, white spots in and around the pancreas itself are seen, with no hæmorrhage, vascular congestion or leucocytic infiltration.

### SIGNS AND SYMPTOMS

In preparing this paper I have been greatly impressed by the marked diversity of the signs and symptoms occurring in this disease, but by presenting them in a series of tables, it is hoped to demonstrate more clearly the predominant features. Critical and careful study of these will, it is hoped, enable a correct diagnosis to be made in the majority of cases, thus resulting in the appropriate treatment being instituted at the earliest possible moment.

*Age.*—In the series under review, the largest age groups lie between 40 and 70 years of age, the youngest being a girl of 10 years and the oldest being 85 years of age.

TABLE 2

Age					Number of Patients	Percentage
10-19	..	..	..	..	1	.9
20-29	..	..	..	..	3	2.7
30-39	..	..	..	..	7	6.4
40-49	..	..	..	..	22	20.0
50-59	..	..	..	..	29	26.4
60-69	..	..	..	..	31	28.2
70-79	..	..	..	..	16	14.5
80-89	..	..	..	..	1	.9
TOTAL .. ..					110	100.0

*Sex.*—McWhorter (1932) and Abell (1938) found that the sexes were equally affected, but my own figures show a large preponderance of females over males.

TABLE 3

Sex					Number of Cases	Percentage
Males	..	..	..	..	37	33.6
Females	..	..	..	..	73	66.4
TOTAL .. ..					110	100.0

*Obesity.*—In a number of cases obesity has been pronounced but in only 16 cases (14.5 per cent.) was it considered sufficient to be commented upon. It is, however, considered significant to mention that approximately 50 per cent. of cases were overweight.



*Temperature, Pulse and Respiration.*—In 64·5 per cent. of cases the temperature was normal or subnormal and in 89·1 per cent. of cases the temperature was not above 100°F. On the other hand the pulse was definitely accelerated in 82·7 per cent. of cases and was invariably of poor volume and tension. Of course these figures must be viewed in relationship to all the other clinical signs, the duration of illness, the presence or absence of shock, etc., to be of any real value. The absence of fever, combined with a rapid pulse and a high white cell count, is significant.

### PREVIOUS ILLNESSES

Although the attack may commence in apparently healthy subjects, careful questioning will frequently elicit the fact that attacks of similar, but less severe, pain have occurred in the past, suggesting peptic ulcer or gall-bladder disease. A review of the previous illnesses of these 110 patients is shown in the following table, and it will be seen that they are all connected with the gastro-intestinal tract.

TABLE 4

Previous Illnesses	Number of Patients	Percentage
1. Gastric disturbances ..	29	26·4
2. Gall-Bladder Disease ..	43	39·1
3. Gall-stones .. ..	4	3·6
4. Appendicitis .. ..	11	10·0
5. Gastro-Enterostomy ..	1	·9
6. Previous Acute Pancreatitis	1	·9
TOTAL .. ..	89	80·9

It must be clearly understood that this table was compiled from information obtained from hospital records, notes of the family doctor, and the patient's own statement. There is no doubt in my own mind that in quite a large proportion of these cases, the correct diagnosis should have been "a mild attack of acute pancreatitis."

Most authorities state definitely that a cholecystectomy saves the patient from a possible attack of acute pancreatitis, yet two of my patients, H. H. and M. S., had a cholecystectomy performed 2 and 8 years previously. Another patient, G. W., had had a laparotomy for acute pancreatitis 13 years previously and had had a sub-acute attack in 1939.

Twenty-four patients (21·8 per cent.) were X-rayed during their stay in hospital and the following results were obtained :—

TABLE 5

Gall-Bladder Disease .. ..	8 cases (33·3%)
Gall-Bladder Disease with stones ..	10 cases (41·7%)
Normal Gall-Bladder .. ..	6 cases (25%)

"Indigestion" was complained of by 32 cases (29 per cent.) in this series.

## PAIN

The onset of the pain is invariably sudden and this *initial* pain may be due to one or more of the following causes :—

- (1) Associated biliary pathology, e.g., Acute Cholecystitis.
- (2) Rapid inflammatory swelling of the pancreas with stimulation of the nerves in the coeliac plexus and post-parietal peritoneum.
- (3) Early and copious toxic exudate into the peritoneal cavity producing marked irritation of the parietal peritoneum.
- (4) Raised intraductal pressure.
- (5) Trauma.

(a) *Situation*.—The site of the pain varies greatly, and the varying figures quoted in the literature are quite understandable when the following facts are considered :—

- (1) The time between the onset of the disease and admission to hospital, e.g., pain may be primarily epigastric, but soon becomes generalised.
- (2) The extent of involvement of the pancreas, e.g., whole, head, body or tail.
- (3) Presence and amount of free fluid in peritoneal cavity.
- (4) Pain in the right iliac fossa due to secretions leaking through the foramen of Winslow down the right paracolic gutter.
- (5) Patient being nursed in Fowler's position may result in lower abdominal pain but with marked epigastric tenderness.

In this series of cases the pain was localised to the upper abdomen in 91 cases (82·7 per cent.), being primarily epigastric in 60 cases (54·5 per cent.) and becoming generalised in 48 cases (43·6 per cent.) by the time of admission. In 15 cases (13·6 per cent.) the pain was generalised from the onset and the patient was unable to demonstrate the point of maximum intensity. In only 18 cases (16·4 per cent.) did the patient complain of pain over the gall-bladder, whilst in two cases (1·8 per cent.) pain was localised to the left hypochondriac region. Umbilical pain was primarily present in five cases (4·5 per cent.), in the right iliac fossa in three cases (2·7 per cent.) and in the left iliac fossa in one case (0·9 per cent.). Praecordial pain was also complained of in one case (0·9 per cent.). Another very important feature of this pain is its tendency to radiate. Broadly speaking radiation occurs in over 60 per cent. of all the cases and the usual sites are the costo-vertebral angles, and the shoulder tips. Severe backache in the lower thoracic region was a marked feature in only 38 cases (34·5 per cent.). This backache may be in the midline or in one or other costo-vertebral angle ; the left being by far the most significant. In 12 cases (10·9 per cent.) there was pain in the shoulder tips, being three times commoner in the right than in the left.

Pain radiating across the epigastric region from right to left is a most important sign and is practically pathognomonic of this disease.

The next question is this : " Is the site of the pain determined by the portion of the pancreas affected ? " A categorical answer cannot be

given because of the numerous factors involved, but this can almost certainly be said, "that where the whole pancreas is involved, the pain usually extends right across the abdomen, but if the head or tail is chiefly affected, other things being equal, the pain is situated in the right hypochondriac and right costo-vertebral regions or the left hypochondriac and left costo-vertebral regions respectively." The referred pains are merely an indication of the irritation of the peritoneal and diaphragmatic areas by the serous exudate.

(b) *Severity*.—In most of the literature, pain which is present in 100 per cent. of cases, is described as sudden, agonising, persistent, colicky or stabbing, but it would be most misleading to expect this in every case. In this series, the pain was of intense severity in 24 cases (21·8 per cent.) and in three of these, it was so severe as to awaken the patients from sleep. In the remaining 86 cases (78·2 per cent.), the pain, although severe, did not appear to be unbearable and in a few of these cases was actually of a gnawing and burning character. In the majority of cases however, it is usually of such severity that it warrants the use of morphine which may only partially relieve it. I personally have abandoned the use of morphine in this disease as it either did not control the pain or it had to be given in very large doses.

From a close study of this series, I have come to the conclusion that the severity of the pain depends upon one or more of the following factors :—

- (1) the degree of obstruction at the ampulla of Vater ;
- (2) the extent of the pancreatic involvement ;
- (3) the amount of pancreatic hæmorrhage ;
- (4) the amount of the serous exudate ;
- (5) the extent of the involvement of the retro-peritoneal tissues ;
- (6) the concomitant biliary pathology especially if "acute" ;
- (7) presence of local or general peritonitis.

(c) *Type*.—On careful questioning the patient frequently admits to similar but less severe attacks, in some cases over a period of years. In my youngest case (a female aged 10 years) she had had four severe attacks over a period of five months, which lasted for half an hour and made the child scream with pain. Frequently there is also a previous history of biliary colic which may be accompanied by intermittent jaundice.

In 99 cases (90 per cent.) the pain, whether epigastric, upper abdominal or generalised, continued without intermission, but in 11 cases (10 per cent.) paroxysms of still more severe pain were felt. Of these 11 cases, eight definitely had gall-stones, whilst the remaining three showed evidence of gall-bladder disease. In one case which complained of severe paroxysmal pain, a stone was found in the ampulla of Vater at post mortem. These paroxysms of pain may well be due to an attempt to pass a gall-stone from the ampulla of Vater into the duodenum and should this be successful, the paroxysms will cease and the stone will therefore

not be found at operation or post-mortem. Another cause of this paroxysmal pain may be further hæmorrhage into the pancreas and peripancreatic tissues from the blood vessels whose walls have been digested.

### IMPORTANCE OF THE TYPE OF PAIN IN DIFFERENTIAL DIAGNOSIS

(1) *Acute Cholecystitis*.—In this disease, the pain is usually confined to the right hypochondriac area and frequently radiates to the right scapula or to the right shoulder tip. Also, we frequently get a history of recurrent biliary colic with intermittent jaundice.

(2) *Acute Intestinal Obstruction*.—The spasmodic pain of acute intestinal obstruction does not occur in acute pancreatitis, but the pain may be continuous and be referred to the region of the umbilicus. As the toxæmia of intestinal obstruction progresses, the pain diminishes, but the vomiting continues. Pain in the back is felt only very rarely in intestinal obstruction.

(3) *Perforated Peptic Ulcer*.—The striking features of the pain in perforated peptic ulcer are :—

- (i) the severity, which doubles up the patient and is increased by movement;
- (ii) pain referred to the supraspinous fossa or summit of the shoulder;
- (iii) partial relief of pain in the "second stage."

(4) *Aneurysm*.—In differentiating the pain due to abdominal aneurysm or dissecting aneurysm of the abdominal aorta, it is to be noted that this pain is neuralgic in character or may simulate renal colic.

(5) *Acute Coronary Artery Occlusion*.—Substernal pain or pain radiating to the neck or left arm is strongly suggestive of this condition.

### SHOCK

It is generally accepted that the severe pain is almost invariably accompanied by shock or collapse which may be so profound as to prove fatal in a matter of hours. The cause of this rapid collapse is not clear, but it may be due to (1) the pressure of blood on the semilunar ganglia and celiac plexus, (2) the absorption of toxins derived from the protein digestion in the abnormal pancreas, (3) reflex disturbance mediated through the nerves of the region, (4) the severity of the hæmorrhage, or (5) the stripping of the parietal peritoneum off the posterior abdominal wall.

Fifteen cases (13·6 per cent.) of this series were suffering from profound shock when admitted to hospital. It must however, be observed that in those patients suffering from repeated paroxysms of pain, spontaneous recovery from the primary shock is unlikely to occur and may even be increased.

### NAUSEA AND VOMITING

Vomiting occurs early and is usually unaccompanied by nausea. It is repeated at frequent intervals and may be as often as half-hourly. The vomiting is also forcible in character, but the amount varies greatly. It

consists at first of gastric contents, later of bile and occasionally it contains a trace of blood, but it is never faecal.

It has been pointed out that the absence of bile in the vomit may be an additional finding of great value in the diagnosis of the presence of ampullar obstruction. If the patient has not vomited, aspiration of the duodenal contents is a relatively easy procedure and may serve as a means of determining the patency of the common bile duct.

Vomiting was a pronounced feature in 89 cases (80.9 per cent.) but blood was present in only one case (0.9 per cent.). This blood in the vomit could be due to a co-existing peptic ulcer, blood passing from the pancreatic duct into the duodenum or from an intensely inflamed stomach or duodenum.

Another important point is that the vomiting gradually tends to subside in contrast to the vomiting of acute intestinal obstruction which becomes more marked and eventually stercoraceous. In contrast to this again, the patient with a perforated peptic ulcer may vomit once or twice but no more. In thrombosis and embolism of the superior mesenteric artery, vomiting is early and severe, the vomitus sometimes containing blood, and it is followed by melæna.

#### FLATULENCE

Flatulence was present in 22 cases (20 per cent.) and flatus was expelled both by the mouth and per rectum. It was a very distressing symptom and caused the patients most acute discomfort.

#### BOWELS

Constipation was a recent symptom in 24 cases (21.8 per cent.) but it was never absolute, which is the rule in acute intestinal obstruction. In four cases (3.6 per cent.) the patient complained of diarrhœa, but melæna was not observed in any case of this series, although it has been mentioned by other observers.

#### JAUNDICE

Jaundice may be as high as 43 per cent. (Lewison (1940)) or as low as 10 per cent. (Abell (1938)); the number in this series being 13, giving a percentage of 11.8. The jaundice is usually attributed to an obstruction at the ampulla of Vater, or pressure of the swollen pancreas on the common bile duct.

#### CYANOSIS AND SKIN DISCOLORATION

There may be only slight cyanosis of the lips and ears or it may be widely distributed over the abdomen and limbs. This has been attributed to shallow breathing because of the painful abdominal lesion, to marked shock and cardiac failure, or to toxæmia. Occasionally there is a local discoloration of the abdominal wall around the umbilicus (Cullen's sign) and in the loins (Grey Turner's sign). It is only seen in cases of some 2-3 days' standing and the patches have the appearance of the skin in cases with late extravasation of urine, gas gangrene, or virulent influenzal pneumonia. The discoloured areas are slightly œdematous and the

œdema fades into the surrounding tissues. Their size varies greatly and in one case, described by Blauvelt (1946), it was 5 cms. in diameter. They are usually attributed to the direct action of the pancreatic ferments which escape via the retroperitoneal tissues and pass by the most direct route to the surface, or to the action of the pancreatic lipase carried by the blood stream.

Cyanosis of the lips and ears was present in 6 cases (5.5 per cent.) and discoloration of the flanks in 1 case (0.9 per cent.). As the latter sign only occurs in very acute cases the prognosis is bad, Eliason (1930) putting the mortality at 85 per cent.

In acute coronary occlusion, cyanosis is usually present, but the main distinguishing features are an irregular pulse and præcordial distress.

### ABDOMEN

(a) *Inspection*.—Examination of the abdomen shows that the movements are definitely limited and therefore the breathing is mainly thoracic. In cases with severe epigastric pain the abdomen may be immobile above the umbilicus. In the early stages the contour of the abdomen is that which is normal for the individual, but it soon becomes distended. This abdominal distension was a feature in 29 cases (26.4 per cent.) and was most evident in the epigastric region. It is due to the transverse colon being paralysed and distended with gas, and also to an incomplete ileus. In acute intestinal obstruction the distension is usually more marked and generalised, but it is not present until the very late stages of perforated peptic ulcer.

(b) *Palpation*.—Abdominal palpation demonstrated the presence of extreme local tenderness in 35 cases (31.8 per cent.) and generalised tenderness in 47 cases (42.7 per cent.). A milder type of tenderness was present in the remaining 28 cases (25.5 per cent.) but there is no direct relationship between the degree of tenderness and the type of the pancreatic lesion.

Very careful palpation may determine that there is deep tenderness over the whole of the pancreas, whilst in other cases it may be more marked on the left side of the epigastrium. If the tenderness is chiefly on the right side, then the possibility of co-existing gall-bladder disease must be considered. The most important sign, however, is tenderness in the costo-vertebral angles, especially if this is on the left side. Recoil tenderness is invariably present and is often very marked, especially in the region of the upper abdomen.

In the early stages, the abdominal wall is flaccid. Muscular rigidity is either absent, or only occurs to a very mild degree. This mild degree of rigidity was present in 59 cases (53.6 per cent.) being generalised in 33 cases (30 per cent.) and localised to the epigastrium in 26 cases (23.6 per cent.). In approximately half the cases, the point of maximum tenderness corresponded to the point of maximum muscle spasm.

In the later stages of this disease, the rigidity may be generalised and

severe, but obviously the extent and degree of rigidity must be correlated with the whole of the clinical picture in order to be of value. It is the combination of extreme tenderness and the lack of definite muscular rigidity which is so characteristic; the rigidity which may develop later is due to peritonitis secondary to pancreatic infection.

In acute cholecystitis, muscular rigidity is usually marked in the upper half of the right rectus muscle and in both upper quadrants or even generalised in perforated peptic ulcer.

No tumour is likely to be felt in the epigastric region until the third day (Kröte's sign) and even then the pancreas may not be palpable. This mass may be felt either in the epigastrium or left loin and was present in 17 cases (15·4 per cent.) in this series. The swelling moves little on respiration and often transmits a non-expansile pulsation from the underlying aorta. It may be separated from the liver and spleen by areas of resonance.

In acute cholecystitis, the gall-bladder may be palpable. A small rounded swelling with an expansile pulsation situated usually to the left of the mid-line is present in abdominal aneurysm and a vague mass in dissecting aneurysm of the abdominal aorta. Dinsmore and Nosik (1939) suggest that areas of hyper-æsthesia on the left side corresponding to the segments of T 8-10, possibly even higher, would be found, if sought for, but although I have been unable to confirm this in more than 3 cases (2·7 per cent.) it is of definite significance.

(c) *Percussion*.—There is no alteration in the area of hepatic dullness in acute pancreatitis, but it may be diminished or absent in perforated peptic ulcer. The presence of free fluid may be demonstrated in the peritoneal cavity and may be of such an amount as to give rise to "shifting" dullness. This was present in 8 cases (7·2 per cent.). Morton (1940) and Fallis (1939) have withdrawn this fluid by abdominal paracentesis, the former reporting on a characteristic prune juice fluid and the latter finding blood-stained fluid. Personally I am of the opinion that this method of investigation is quite unjustified.

### Auscultation

Intestinal sounds in acute pancreatitis disappear almost immediately but in acute intestinal obstruction the sounds are easily heard and only disappear at a late stage.

### Rectal examination

This may yield no definite information, but it is extremely tender when there is free irritant fluid in the peritoneal cavity and when peritonitis has developed in the later stages.

### URINE

Changes in the urine are not constant but nevertheless may be important when taken with the other signs and symptoms. The following table shows the abnormalities which occurred in this series:—

TABLE 6  
Urine

	Number of Cases	Percentage
Albumen .. .. .	27	24.5
Blood .. .. .	4	3.6
Bile .. .. .	12	10.8
Sugar .. .. .	14	12.7
Acetone Bodies .. .. .	6	5.4
Increased Urinary Diastase ..	15	13.6
Dysuria .. .. .	7	6.3
Oliguria .. .. .	1	.9

Albuminuria was present in 25 per cent. of cases and in the vast majority was only transient. It could be due to one of the following causes, namely, cardiac failure, shock, toxæmia, fever, renal damage or simply from pressure of the œdematous pancreas on the renal veins. Hæmaturia only occurred in 3.6 per cent. of cases and is probably due to an accompanying nephritis or to severe renal congestion, again due to pressure on the renal veins.

As mentioned above, jaundice was present in 13 cases and in 12 of these, bile was detected in the urine.

If glycosuria is found, it tends to confirm the diagnosis, but this finding is said to be uncommon, probably because death occurs too rapidly. (Proof: in animals, even total removal of the pancreas is not followed by glycosuria for several days.) Its presence undoubtedly demonstrates destruction or temporary non-functioning of the Islets of Langerhans, and as mentioned later, the patient may develop diabetes mellitus, but no such case occurred in this series.

*Urinary Diastase.*—In the healthy subject the concentration of diastase in the urine is usually between 2 and 50 units, but there are marked variations in the figures obtained at different times of the day, owing to polyuria or oliguria.

The daily output of diastase is estimated by multiplying the volume in cubic centimetres of a 24-hour specimen of urine by the diastase index. The figure normally lies between 8,000-30,000 units.

In acute pancreatitis, the first specimen of urine available is taken and in the majority of definite cases, it usually contains 100 or more units per cubic centimetre; lesser concentrations being of little or no significance. The highest figures are usually obtained if the test is performed within a few hours of the acute onset of the disease, but the urinary diastase only rises from 6-24 hours after the rise in blood amylase.

In some definitely proved cases of acute pancreatitis, there is no increase in urinary diastase, especially if the test is performed 14 days after the acute onset. This is almost invariably found in the following types of cases:—



increased blood or urinary diastase and therefore this factor, in conjunction with the foregoing signs and symptoms, is of definite diagnostic value, but a normal diastase index does *not* exclude pancreatitis.

(b) *Hyperglycæmia*.—If the blood sugar rises to over 300 milligrams per cent. the outcome is invariably fatal. In 11 cases (10 per cent.) of this series, no increase in the blood sugar was detected. Shumacker (1940) concluded that at least 2 per cent. of all cases with severe acute pancreatitis acquired diabetes mellitus, and, of those surviving the acute illness, from 3-10 per cent. became subjects of diabetes mellitus.

(c) *Blood Count*.—In this series the maximum recorded white cell count was 38,000 per cubic millimetre and this was in a case of marked pancreatic necrosis. The majority of cases had a count ranging from 6,000-15,000 per cu. mm.

(d) *Blood Calcium*.—Edmondson and Berne (1944) reported that in 72 per cent. of cases the serum calcium was below 9 milligrams per 100 cc. between the 2nd and 15th day of the disease and that the average serum calcium value was the lowest on the 6th day. If the serum calcium level was below 7 milligrams per 100 cc., the prognosis was invariably fatal. At these low levels it is necessary to keep a careful watch for the onset of tetany and to treat it vigorously.

(e) *Plasma, Protein and Prothrombin*.—Lowering of the protein and prothrombin content of the blood during an attack of acute pancreatitis is said to occur, but further investigation is necessary before any definite conclusions can be drawn.

## SPECIAL TESTS

### Loewi's Test

In this series the test was negative in nine out of 14 definitely established cases of acute pancreatitis, whilst being positive in a case of gangrenous cholecystitis.

### Cambridge's Pancreatic Reaction

This is not pathognomonic of acute pancreatitis and is now regarded as so unreliable as to be useless.

## LATE CASES

If the patient is seen at a later stage, the clinical picture is slightly different. Dittler and McGavack (1938) reported on a case of acute pancreatitis complicated by impure auricular fibrillation and flutter, but at autopsy no organic lesion could be found. They therefore concluded that the cardiac condition was due to reflexes from the abdomen. Loeffler and Esseluer (1946) state that acute pericarditis has also been found in several cases. Dyspnoea occasionally occurs and may even amount to air hunger. Hiccup may be present and if persistent, generally indicates a grave prognosis. Two patients (1·8 per cent.) in this series found this a most distressing symptom and both died.

Shifting dullness, uncommon in the early stages, can usually be elicited

TABLE 8

Surgeon's Diagnosis	Number of Cases	Percentage
(1) Acute Pancreatitis .. .. .	46	41.8
(2) Acute Cholecystitis .. .. .	32	29.1
(3) Acute Intestinal Obstruction ..	13	11.8
(4) Perforated Peptic Ulcer .. ..	16	14.5
(5) Acute Appendicitis with Peritonitis	2	1.8
(6) Coronary Thrombosis .. .. .	1	.9
TOTAL .. .. .	110	99.9

Other observers have made the following observations :—

TABLE 9

Author	A.P.	G.B.D.	App.	P.P.U.	A.I.O.	M.T.	C.T.
	%	%	%	%	%	%	%
Morton and Widger (1940)	17	—	—	—	—	—	—
Lewison (1940) .. .. .	13	70	10	—	—	—	—
Morton (1940) .. .. .	17	43	5	27	8	5	5
Fallis (1939) .. .. .	30.8	—	—	—	—	—	—
Abell (1938) .. .. .	12	—	—	—	—	—	—

## Key

A.P. = Acute Pancreatitis

P.P.U. = Perforated Peptic Ulcer

G.B.D. = Gall-Bladder Disease

A.I.O. = Acute Intestinal Obstruction

App. = Appendicitis

M.T. = Mesenteric Thrombosis

C.T. = Coronary Thrombosis

Other conditions which must also be considered are :—(1) pneumonia, (2) acute nephritis, (3) ruptured ectopic pregnancy, and (4) spontaneous rupture of the common bile duct.

## TREATMENT

(1) *Prophylactic*.—As Cole (1938) pointed out, gall-bladder disease is far too common, and acute pancreatitis too uncommon, to justify cholecystectomy merely in the endeavour to prevent acute pancreatitis. Chronic alcoholism, obesity and any disease of the biliary tract should be treated.

(2) *Conservative*.—Modern treatment tends to be conservative, and certainly the figures published of cases so treated show a definite decrease in the mortality rate. Evidence of old fat necrosis discovered at a later operation as well as the biochemical tests mentioned above, definitely prove that conservative treatment has been successful. In acute pancreatitis due to mumps, operation is never indicated and recovery is usually complete within a week. If conservative treatment is decided upon, frequent and detailed clinical examination of the patient is essential with hourly recordings of the pulse rate and blood pressure. Forty-one of this series (37.3 per cent.) were treated by conservative methods. Of these, 30 cases (73.2 per cent.) made an uninterrupted recovery, whilst 11 cases

determine the type and degree of pancreatitis. Atropin Sulphate, given in as large doses as  $\frac{1}{50}$  gr. 6-hourly for 24 hours, acts as an excellent antispasmodic and proportionately smaller doses may be given later. This drug is also extremely useful if there is excessive sweating. According to Smead (1940) small doses of ephedrine 4-hourly are also useful if vascular collapse is present. Popper (1933) described 3 cases in which he relieved pain by the paravertebral injection of the 8th-10th dorsal nerves with novocaine, and partly ascribed these good results to the local vasodilatation produced by blocking the sympathetic innervation to the pancreas.

Considerable quantities of calcium may be present in the lesions in cases of acute pancreatic necrosis and it is logical to assume that a plentiful supply of available calcium is desirable in order to facilitate the formation of calcium soap in situ without undue depletion of serum calcium and the possible onset of tetany. This may be given in the form of a 10 per cent. solution of calcium gluconate intravenously in 10 cc. doses. Lastly, chemotherapy and penicillin therapy should be employed in full doses to prevent local infection of the necrotic pancreatic tissues and in an attempt to prevent infection spreading into the peritoneal cavity.

### DIET

It is essential that intravenous therapy should be continued for 3-4 days and that nothing be given by mouth in an attempt to inhibit the activity of the pancreas. The intake of food must be resumed very carefully and easily assimilable carbohydrates should be given, e.g., milk, milk puddings, orange juice, glucose, honey, carrots, white of egg, etc. Fat is not permissible for several weeks and meat is forbidden as the protein intake must be limited.

### LENGTH OF STAY IN HOSPITAL

TABLE 10

Time	Number of Patients	Percentage
Less than 1 week .. ..	2	6.6
1-2 weeks .. ..	13	43.3
2-3 weeks .. ..	9	30.0
3-4 weeks .. ..	4	13.3
4-8 weeks .. ..	1	3.3
8-12 weeks .. ..	1	3.3
TOTAL .. ..	30	99.8

It will be noted that with conservative treatment 24 (80 per cent.) of the 30 cases which survived were discharged from hospital within three weeks.

Before turning to the discussion of operative treatment, it should be emphasised that it is unwise to give or to proceed with conservative treatment if the following conditions are present, and early operation

should be advised :—(1) persistent fever or development of fever along with other abdominal signs, (2) spreading peritonitis, (3) pancreatic necrosis, (4) distension of lesser peritoneal cavity, (5) enlargement of the gall-bladder, (6) jaundice, or (7) no response to conservative treatment.

### OPERATIVE TREATMENT

Operation was previously advised in cases of acute pancreatitis for the following reasons :—

- (1) To remove the cause, e.g., gall-stones and to drain the bile passages.
- (2) To relieve the tension about the pancreas by incising its peritoneal covering.
- (3) To remove the fluid from the greater and lesser sacs.
- (4) To provide drainage from neighbourhood of gland.

As will be seen from the ætiology, the cause of acute pancreatitis is not definitely known, and even if gall-stones are present they may not be the determining factor. Provided that there is no stone in the ampulla of Vater, drainage of the biliary tract and pancreatic ducts can be stimulated by duodenal suction.

Incision of the peritoneal covering of the pancreas does not relieve the tension completely because the acini have their own fibrous capsule and it is impossible to operate on them individually. The removal of the hæmorrhagic fluid from the peritoneal cavity also seems to be unnecessary. Ireneus (1941) found that the hæmorrhagic exudate in animals with acute hæmorrhagic pancreatitis was not toxic on the intra-peritoneal injection of 2-3 cc. into white mice or on intravenous injection into dogs.

### Laparotomy as a Diagnostic Procedure

If a definite diagnosis cannot be made from any acute abdominal condition requiring an emergency laparotomy, this must be performed. If œdema of the pancreas or an acute hæmorrhagic pancreatitis is observed, then the abdomen should be quickly but very carefully closed and conservative treatment instituted as detailed above.

### Details of Operative Procedures

In 69 cases (62·7 per cent.) operation was performed, and of these 28 died, giving a mortality rate of 40·6 per cent.

#### Anæsthetic Used

TABLE 11

Anæsthetic	No. of Patients	Percentage	Deaths
Gas, Oxygen and Ether	51	73·9	21
Open Ether .. ..	14	20·3	5
Spinal .. .. .	4	5·8	2
TOTAL ..	69	100·0	28

This table, however, gives no indication of the clinical condition of the patient when submitted to operation. There is, however, no doubt in my mind that these cases should have their anæsthetic administered by a consultant anæsthetist and that the practice of House Surgeons giving the anæsthetic to emergency cases should be whole-heartedly condemned.

Various types of operations have been performed in acute pancreatitis and those employed in this series are detailed in the following table:—

TABLE 12

Type of Operation	No. of Cases	Deaths	Mortality
Laparotomy .. .. .	28	8	28.6%
Laparotomy with suprapubic drainage ..	4	1	25.0%
Laparotomy with drainage of lesser sac ..	8	5	62.5%
Laparotomy with drainage of lesser sac and suprapubic drainage .. ..	2	1	50.0%
Laparotomy with cholecystostomy ..	7	4	56.3%
Laparotomy with cholecystostomy and suprapubic drainage .. ..	2	1	50.0%
Laparotomy with cholecystostomy and drainage of lesser sac .. ..	10	6	60.0%
Laparotomy with cholecystostomy and drainage of Rutherford Morrison's pouch .. .. .	2	Nil	Nil
Laparotomy with drainage of posterior abdominal wall .. .. .	1	1	100.0%
Laparotomy with cholecystectomy ..	4	1	25%
Laparotomy with cholecystectomy and choledochostomy .. .. .	1	Nil	Nil

*N.B.*—It will be noted that laparotomy and laparotomy with suprapubic drainage have the lowest mortality, namely, 28 per cent. In cases in which the gall-bladder was also operated upon, and also when the lesser sac was opened, the mortality rose to 50 per cent. or over. In the three cases which recovered after drainage of the lesser sac, the duration of the symptoms had been longer than 24 hours.

The pancreas is an extraperitoneal organ and therefore if the lesser sac is opened and the peritoneal covering of the pancreas incised, the pancreatic secretions and products of protein metabolism are allowed to escape into the general peritoneal cavity. The great absorptive powers of the peritoneum are well known and therefore the dangers of profound toxæmia are greatly increased by this interference. The obvious conclusion to come to is that it is advisable to interfere operatively as little as possible. Certain features, however, may make it essential to proceed, e.g., marked distension and inflammation of the gall-bladder which may go on to rupture and cause biliary peritonitis. In these cases cholecystostomy is indicated. Jaundice, because it is of the obstructive type, is also an indication for cholecystostomy. Only in rare cases should choledochostomy be performed in order to remove a stone in the ampulla of Vater or

common bile duct. This should be attempted if the patient's general condition is good and the common bile duct much distended and easily accessible. Should choledochostomy appear difficult, a rapid cholecystostomy will suffice to decompress the biliary system. Cholecystectomy should be avoided if possible because cholecystenterostomy may be necessary later and also it is accompanied by a great deal of shock in an already ill patient. Later there is also the danger of an increased biliary pressure.

In the absence of gall-stones or jaundice, dilation or thickening of the duct, one is rarely justified in exploring the common bile duct, but should this be necessary, the following points made by McWhorter (1932) are very useful in determining the subsequent treatment :—

- (1) If the outlet of the common bile duct is dilated, prolonged drainage is unnecessary.
- (2) If the outlet is partially or completely obstructed due to local congestion, do *NOT* dilate because of the danger of increased swelling. If possible a tube should be inserted into the common bile duct through the sphincter of Oddi into the duodenum. This prevents a further reflex of bile into the pancreatic duct.

Pancreatic necrosis or suppuration is another indication for drainage and may best be done through the loin or costo-vertebral angle. Drainage of fluid in the lesser sac is advisable as it may prevent the development of a pseudocyst and may be carried out through the gastro-colic or gastro-hepatic omentum.

If a retroperitoneal involvement is present as indicated by surface discoloration, incisions are made into the loin. In very rare cases, pancreatic lithiasis is present and it is necessary to remove the stone by a transduodenal incision exposing the ampulla of Vater, which is split, and the stone removed with forceps.

### Pancreas

Various parts of the pancreas were seen at operation to be the site of the initial lesion, but in only 33 cases (47·8 per cent.) was the whole of the organ involved. In only two cases (2·9 per cent.) was the disease confined to the tail whilst the remainder were about equally divided between the rest of the pancreas.

### Fat Necrosis

Fat necrosis was found in 55 cases (79·7 per cent.) and was invariably extensive over the omentum, mesentery and parietal peritoneum.

### Free Fluid

Free fluid was found in 13 cases (10·8 per cent.) mainly in the lesser sac and around the gall-bladder. This fluid was chocolate-coloured in 5 cases (7·1 per cent.), blood-stained in 7 cases (10·1 per cent.) and serous

in 1 case (1·4 per cent.). McWhorter (1932) found free fluid in 60 per cent. of his cases, the majority being blood-stained.

### Gall-Bladder

The gall-bladder appeared normal in 20 cases (29 per cent.) but was diseased in the remaining 49 cases (71 per cent.), the degree of involvement being shown in the following table :—

TABLE 13

State of Gall-Bladder	No. of Patients	Deaths	Mortality
(1) Apparently healthy Gall-Bladder ..	20	8	40%
(2) Apparently healthy Gall-Bladder with Gall-Stones .. .. .	13	4	30·8%
(3) Acute cholecystitis .. .. .	13	5	38·5%
(4) Acute cholecystitis with gall-stones ..	3	3	100·0%
(5) Chronic cholecystitis .. .. .	5	4	80·0%
(6) Chronic cholecystitis with gall-stones	13	4	30·8%
(7) Empyema of gall-bladder with gall-stones .. .. .	2	—	Nil
TOTAL .. .. .	69	28	

From the table it will be seen that gall-stones were present in 31 cases (44·9 per cent.) and in only 1 case was a stone found in the ampulla of Vater at operation. If there is no contra-indication to operation, all cases in which gall-stones are demonstrated should be treated surgically, as their removal may prevent a further attack. This operation should be performed preferably 3 months after all the acute symptoms have subsided.

Other findings at operation were marked œdema of the posterior abdominal wall in 5 cases, 3 of which died. In one case a chronic gastric ulcer was present and in another a duodenal ulcer.

### POST-OPERATIVE TREATMENT

When the patient returns from theatre he should be given the usual treatment for post-operative shock and this should be followed by the strict régime laid down under conservative treatment.

### Post-Operative Complications usually associated with Acute Pancreatitis

(1) *Burst Abdomen*.—This may be guarded against to a certain extent by perfect peritoneal apposition, the use of non-absorbable sutures, with interrupted sutures for the muscles, and the supporting of the wound by means of laparotomy corsets. Should the ferments escape on to the surface, the skin may become digested and this is best guarded against by applying paraffin molle ointment containing 2 per cent. hydrochloric acid, paint daily with Whitehead's varnish, or Lanolin ointment containing 1 per cent. acetic acid applied liberally.

## ACUTE PANCREATITIS

(2) *Thrombosis of Splenic and Mesenteric Veins*.—Very little can be done for this complication except the administration of heparin, or dicumerol and penicillin to counteract sepsis. The outcome is invariably fatal.

(3) *Pancreatic Insufficiency*.—This is treated by blood transfusion and pancreatic extracts. Pancreatinum may be given orally in doses of 3-5 grains, 2-3 hours after a meal. This is to prevent its destruction by the acid in the gastric juice. This white- or buff-coloured powder contains the enzymes, trypsin, lipase and amylase. Peptonised foods in the form of peptonised milk, beef tea and Benger's food may also be given. Pancreatinum may also be given in the form of an enema in 4 oz. doses in equal parts of milk and beef tea. Other proprietary preparations are: dipantrin, panacoids, panteric tablets and zymine. These extracts may have to be continued for several months and estimations of serum amylase and lipase give some guide as to the extent and progress of the deficiency.

(4) *Diabetes Mellitus*.—This is treated on the usual lines.

(5) *Pseudocyst of Pancreas*.—This is dealt with by drainage and a counter-incision in the left loin.

(6) *Pancreatic Fistulae*.—Bufalini (1947) describes an operation for a persistent fistula by which he converts it into an internal drainage by using the fistulous track and anastomosing the cutaneous opening with an abdominal viscus. Persistent cases may be cured by the insertion of radium into the tract.

## MORTALITY

In this series 25 males were operated upon and 15 died, giving a mortality of 60 per cent.; of 44 females 13 died, giving a mortality of 29.5 per cent., i.e., a total mortality of 40.6 per cent. This compares favourably with other observers as seen on the following table:—

TABLE 14  
Mortality

Author	Operative Treatment	Conservative Treatment
Fallis (1939) .. ..	46.2%	6.3%
Pratt (1940) .. ..	54%	25%
Lewison (1940) .. ..	50% (E.)	—
Morton (1940) .. ..	49.03%	—
Eliason (1930) .. ..	80% (E.)	—
Finney (1933) .. ..	37%	—

(E=Emergency Operation.)

It may also be noted that no patient under 40 years of age died.

Of the 42 cases which were operated upon as emergency cases, 21 died and 21 recovered and of the 19 cases which were not treated as emergencies but later operated upon, only 7 died.



Of the 38 cases operated upon with symptoms of less than 24 hours duration, 17 died and of these, 12 were subjected to a more extensive operation than a simple laparotomy. Twenty-one of the cases which recovered were submitted to the following operations:—

TABLE 15

Laparotomy and Laparotomy with Suprapubic Drainage	..	12 cases
Cholecystostomy	.. .. .	4 cases
Cholecystostomy and Drainage of Lesser Sac	.. .. .	2 cases
Drainage of Lesser Sac	.. .. .	1 case
Cholecystectomy	.. .. .	2 cases

Of the 27 patients whose symptoms had been present for 1-4 days, 19 recovered and 8 died, but it will be noted that only one of these 8 fatal cases had a simple laparotomy.

### CONCLUSIONS

*Ætiology.*—It must reluctantly be admitted that in spite of all the present available evidence, not one of the current theories of the genesis of acute hæmorrhagic pancreatitis adequately explains the mechanism of its production. As Smyth (1940) pointed out, the solution of this problem is more likely to be found in the experimental studies in which the earliest stages of the disease can be investigated rather than by examining the materials obtained at autopsy.

*Pathology.*—It will be noted that the associated pathology is invariably confined to the biliary and gastro-intestinal tracts. Hæmorrhage into the pancreas and fat necrosis is not pathognomonic of this condition.

*Signs and Symptoms.*—If a stoutish elderly patient of either sex with a previous history of indigestion has an acute attack of severe upper abdominal pain, marked epigastric tenderness without muscular rigidity, upper abdominal distension, distressing flatulence, frequent vomiting, a rapid pulse of extremely poor volume and tension, increased urinary diastase, and a fall in serum calcium level; acute pancreatitis should be suspected. One should, however, be cautious in diagnosing acute pancreatitis if the patient already has a laparotomy scar.

*Treatment.*—In common with other observers, there is no doubt in my own mind that conservative treatment is definitely preferable, but it is suggested that the following are definite indications for surgical intervention after suitable pre-operative treatment:—

- (1) Uncertainty in diagnosis.
- (2) Failure to respond to conservative treatment as shown by failing circulation and evidence of renal damage.
- (3) Traumatic pancreatitis with involvement of other organs.
- (4) Evidence of spreading peritonitis—biliary or suppurative.
- (5) Deterioration of the patient's general condition which could be attributed to necrosis or suppuration of the pancreas.
- (6) Jaundice.
- (7) Associated biliary tract disease.

- (8) Retroperitoneal involvement as shown by discoloration in the loins.
- (9) Distension of lesser peritoneal cavity or pseudocyst of the pancreas.
- (10) Pancreatic fistula—after prolonged conservative treatment has failed.

High serum amylase indicates severe pancreatic disease but this in itself is *not* an indication for operation because the decision to operate must be based on clinical grounds.

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## SAYINGS OF THE GREAT

“Not gone, but dead before.”—*Confucius—on a recently retired and uninspired Professor.* (Submitted by Douglas Robb, F.R.C.S.)

“Confidence and hope do more good than physic.”—*Galen.* (Submitted by C. Allan Birch, M.D., F.R.C.P.)

“Everything can always be done better than it is being done.”—*Henry Ford.* (Submitted by C. Allan Birch, M.D., F.R.C.P.)

“No idea is wholly new: what is new is getting people to adopt it and to act upon it.”—*Harvey Cushing.* (Submitted by Professor Lambert Rogers.)

# ACUTE SUBDURAL AND EXTRADURAL HÆMATOMA IN CLOSED HEAD INJURIES

Hunterian lecture delivered at the Royal College of Surgeons of England  
on  
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by

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## INTRODUCTION

OVER SIXTY YEARS AGO Jacobson (1886) wrote what is still the finest clinical description of middle meningeal hæmorrhage. Its general features had, of course, been known before this and several fundamental contributions to the subject had been made by surgeons whose names are particularly revered in this College. Percival Pott wrote a little book on head injuries in 1759 in which he urged the importance of early operation for extradural hæmorrhage. John Hunter, in 1786, called attention to the difficulties of diagnosis in head injuries—" . . . However, as we cannot tell for certain at the time whether the symptoms arise from concussion, compression, or from extravasation of blood it may be more advisable to trepan, as the operation can do no harm. . . . In all cases of violence attended with compression, either from fracture or not, the trepan is absolutely necessary." This bold advocacy of exploration earned the disapproval of Palmer who edited his works in 1835.

Sir Charles Bell, in his "Surgical Observations" of 1817, demonstrated how a sharp blow to the head could tear the dura from the bone and so initiate the train of events which led to the formation of an extradural clot. Jonathan Hutchinson (1867) drew attention to the importance of pupillary changes which accompanied the resulting cerebral compression, and Erichsen (1884) described more fully the hydrodynamics of the developing clot.

In recent years we have had admirable reviews by MacKenzie (1938), Munro and Maltby (1941) and others, but it is to these earlier writers that we are indebted for nearly all that is known to-day of this complication.

The surgical significance of subdural hæmatoma has been increasingly recognized in recent years, due mainly to the work of Trotter (1915), Putnam and Cushing (1925) and later Munro (1938, 1942).

Exploratory burr holes have been increasingly employed as a diagnostic measure, so much so that we are told that though the clinical picture of a surface hæmatoma is frequently diagnostic, a doubtful diagnosis may be readily confirmed or refuted by exploration through suitably placed burr holes.

There would appear, therefore, at first sight, little more to be said on this subject were it not for the fact that the mortality of these hæmatomas

remains very high. In earlier days undiagnosed cases and post-operative infections were chiefly responsible, and one would naturally assume that, with extradural hæmatomas especially, the increasing recognition of the syndrome, the readier resource to exploratory burr holes and improved operative technique would have resulted in a lower mortality. Yet in most clinics when those cases diagnosed only at autopsy are included, it is still about 50 per cent. Nor are the results of this series any exception: for extradural hæmatoma it was 47 per cent., and for acute subdural hæmatoma 62 per cent.—and this in circumstances where all cases came under neurosurgical care from the outset.

It is obvious, therefore, that there remain many unsolved problems, and this lecture is mainly concerned with a closer enquiry into the reasons for this high mortality and with ways in which it might be reduced.

### *Case Material*

Over the seven years 1940-1947 there were admitted to the Radcliffe Infirmary, Oxford, and the Military Hospital for Head Injuries, Oxford, 34 cases of extradural hæmatoma and 21 cases of acute subdural hæmatoma (excluding those due to missile wounds). The diagnosis was made either at operation or at autopsy. Within the same time 36 other cases were explored for a hæmatoma with negative results and their final diagnoses are also considered.

A follow-up has been conducted on those patients who recovered, and also included in this section are 12 others admitted to the Military Hospital for assessment after they had received their initial treatment elsewhere.

### *The Clinical Problem*

What is the essential diagnostic problem with which we are confronted? A patient has survived for some hours after his injury, but fails to improve, or having begun to recover, shows a regression in his conscious level or develops fresh signs in the central nervous system. Is a clot developing and if so, where is it and is it extradural, subdural or indeed intracerebral? There are certainly many cases in which the march of events leaves no doubt as to the diagnosis and the need for exploration; but in treating head injuries it soon becomes apparent that there are other cases of hæmatoma in which the clinical picture is far from typical and also that there are a number of other complications of head injury whose clinical signs exactly mimic the classic picture of hæmatoma.

As a general rule, once a patient who has had a head injury begins to improve, there is a steady march towards recovery although there may be transient set-backs and at times progress may seem to be arrested for hours, or in the more severe head injuries, for days. A progressive deterioration in the patient's condition however, particularly after the first twelve hours, suggests a complication of which a likely cause is hæmorrhage. We find therefore that the predominant features in the diagnosis of a surface hæmatoma may be divided into three groups: (1) a deterioration in the

conscious level of the patient once recovery has begun ; (2) the onset of symptoms and signs of cerebral compression ; and (3) the development of fresh signs in the central nervous system.

In this series, 79 patients were explored in the early days after injury on a presumptive diagnosis of hæmatoma. Table I shows the final diagnoses based either on the operation or the autopsy findings. Despite the policy during this period of exploration only after clinical observation had strongly suggested a surface hæmatoma, in nearly half the cases—36 of the 79—the diagnosis was wrong and within this period three cases of extradural hæmatoma and four of acute subdural hæmatoma came to autopsy without exploration. Such findings indicate the difficulty of the problem and some of the diagnostic possibilities which have to be considered.

TABLE I  
EXPLORATION FOR SURFACE HÆMATOMA—79 CASES

Final Diagnosis	Lived	Died	Total
1 Acute Extradural Hæmatoma	17	9	26
2 Acute Subdural Hæmatoma ..	9	8	17
3 Cerebral Contusion and Lacera- tion .. .. .	4	15	19
4 Intracerebral Hæmatoma ..	—	4	4
5 Subdural Hygroma .. ..	2	1	3
6 "Low Pressure State" ..	2	—	2
7 Cerebral Fat Embolism ..	—	1	1
8 External Hydrocephalus ..	2	—	2
9 Cerebral Œdema .. ..	1	—	1
10 Cerebral Aneurysm .. ..	—	1	1
11 Thrombosis of Carotid Artery	1	—	1
12 Undetermined .. .. .	2	—	2
	40	39	79

A further discussion on these other complications of head injury are beyond the scope of this lecture, but the cases of cerebral contusion and intracerebral hæmatoma will be referred to again when discussing the operative management of the surface hæmatomas.

#### EXTRADURAL HÆMATOMA

The incidence among the civilian cases of head injury admitted to the Radcliffe Infirmary Accident Service was 1 per cent., a figure similar to that given by Rowbotham (1942).

Including those diagnosed only at autopsy, there were 34 cases in this series. The age incidence and the trivial nature of the head injury sustained by many of the patients should be noted. All the 24 civilian patients (which comprise an unselected group) were between five and forty-six years old, which confirms the findings of previous writers that extradural hæmatoma is rare in infants and old people. In just over half the cases the type of injury sustained was a local blow to the temple, or a minor cycle accident or fall. The relatively local nature of the injury was also reflected by the short duration of initial unconsciousness in many patients; thus, of the 29 patients with an acute extradural hæmatoma, seven did not lose consciousness initially at all and 13 others were unconscious for less than one hour.

It became apparent on reviewing these cases that three clinical groups could be recognized.

*Group 1 (20 cases).*—These cases conform to the classical description of the lesion. Thus, after a head injury attended by a short period of unconsciousness, there is a lucid interval (in this series varying from half-an-hour to three days) during which time the patient is well, or, at the most, complaining of headache and nausea. This is followed by progressive impairment of the conscious level and, in some cases, contralateral motor signs and ipsilateral dilatation of the pupil. Although a definite lucid interval was present in only 11 of these cases, included in this group are seven cases where consciousness was not lost initially, but there was subsequent deterioration, and two cases of depressed fracture of the skull where operation was performed on account of local signs, although there had been a satisfactory recovery of consciousness. The diagnosis in many of these cases is fairly straightforward, and the need for exploration apparent in all. The main difficulties are encountered in the other two groups.

*Group 2 (9 cases).*—In these cases there is no lucid interval. The head injury is more severe, full consciousness is not regained, and evidence of advancing cerebral compression has to be sought against a background of the effects of the cerebral contusion, which may vary from a mild confusion to deep coma. In such cases it is the development of fresh signs and further lowering of the conscious level of the patient which lead one to suspect a hæmatoma.

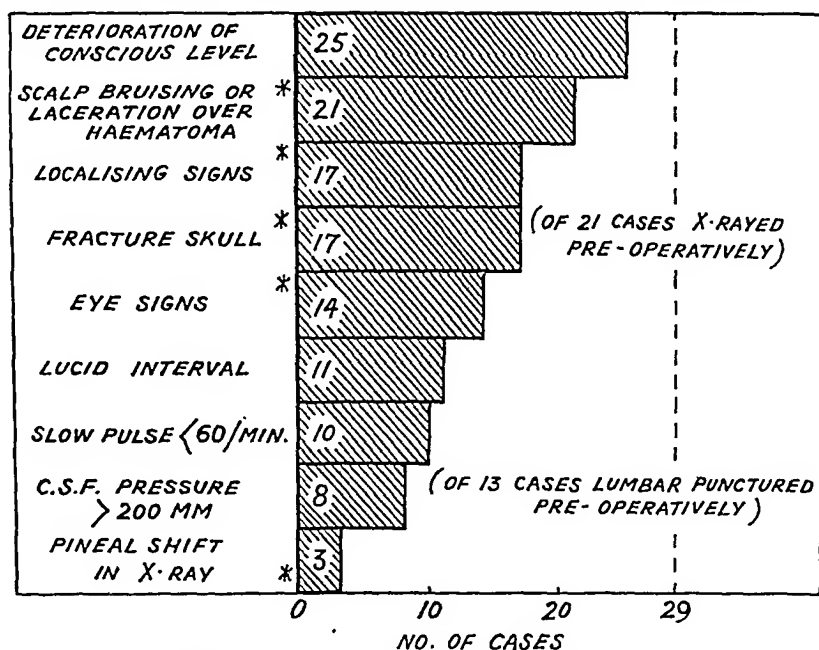
*Group 3 (5 cases).*—A few cases run a "sub-acute" course, a syndrome, which does not seem to have been well recognized in the past. There were five such cases in this series. They came to operation 10-29 days after injury. As they did not present an acute problem in the early days after head injury, they will be considered separately elsewhere, the first two groups comprising the acute cases.

#### *Clinical signs in Acute Extradural Hæmatoma—29 cases*

The incidence of the main signs is summarized in Table II.

*Deepening Coma.*—It will be seen that a deterioration of the conscious level of the patient is the most constant sign, and this stresses the importance of making accurate observations on the mental state of all patients after head injury at each examination. So often in coming to this decision the surgeon must rely on the previous observation of others that an account of a patient's replies to questions and of his reaction to painful stimuli is far more valuable than the use of terms such as "semi-coma," and "partly responding," which cannot be defined

TABLE II  
SIGNS IN 29 CASES OF ACUTE EXTRADURAL HÆMATOMA



\* Correctly indicating the site of the hæmatoma

precisely and depend more on the observer's terminology than on the patient's mental state. Only four patients in this series did not show this change; of these, two remained in deep coma from the time of accident until death, and two had only local signs associated with depressed fracture of the skull and were operated on for this reason.

Observe that a true lucid interval was present in only 11 of the 29 cases although in seven more there was no loss of consciousness initially. The importance of a lucid interval in the diagnosis of an extradural hæmatoma is so firmly entrenched in surgical teaching that it is worth emphasizing that a considerable proportion of these cases had nothing resembling a lucid interval. Moreover, a lucid interval was present in half the subdural cases and in nine of the 36 cases with "negative

explorations" previously mentioned. The true value of a lucid interval lies in the fact that it signals clearly the onset of a complication and usually the need for exploration, but by itself cannot be considered diagnostic of a surface hæmatoma; nor does its absence exclude the possibility.

*Scalp Marks.*—These are extremely useful in lateralising the hæmatoma. A local bruise or laceration of the scalp overlay the hæmatoma in 21 cases. In two cases the only mark present was on the opposite side to the hæmatoma, and multiple bruising was present in three cases; three showed no local mark. A careful inspection of the scalp may therefore be of great assistance and this should be repeated on the operating table after the whole head has been shaved.

*Localising Signs.*—Localising signs such as a hemiparesis or dysphasia are usually reliable. Twelve of the 21 patients with temporal hæmatomas and the one with a parietal hæmatoma developed a contralateral hemiparesis and in a third of the patients with left-sided hæmatomas, dysphasia was also present. In the four frontal cases, a contralateral hemiparesis was present in two and persistent conjugate deviation of the eyes to the opposite side in one. Only one of the three cerebellar cases developed appropriate localising signs, i.e., nystagmus. "False" localising signs were rare in supra-tentorial hæmatomas and were seen in only one patient (Jacksonian epilepsy on the homolateral side).

In two of the cerebellar cases there were signs suggestive of a lesion in the cerebral hemisphere and in both these cases, as will be shown, there was severe frontal lobe contusion in addition to the posterior fossa hæmatoma.

I recently saw a case where a left homonymous hemianopia had developed in association with a right temporal hæmatoma. The clot was successfully evacuated but the hemianopia was still present when the patient was last seen four months later. It used to be said that the presence of an homonymous field defect indicated an intrinsic lesion, but it is now well recognised that if a tentorial pressure cone develops the posterior cerebral artery may be kinked over the sharp edge of the tentorium and produce hæmorrhagic infarction of the corresponding occipital lobe (Meyer, 1920); or if the temporal lobe is enlarged or pushed medially it may compress the optic tract between it and the crus (Traquair, 1927). Either of these alternatives may obtain in an extradural hæmatoma.

*Eye Signs.*—Development of inequality of the pupils or a frankly dilated pupil on the side of the lesion is a reliable sign and was seen in 10 cases; a definite oculomotor nerve paresis was present in four others (one with a ptosis on the opposite side as well). One case showed a bilateral ptosis alone and one of the cerebellar cases developed a unilateral dilated pupil.



In a few cases the oculomotor nerve is damaged at the time of injury, and in this event the patient will present at the outset with a complete palsy. In other cases, study of autopsy specimens shows that if the clot extends along the floor of the middle fossa it may compress the nerve as it runs to gain the superior orbital fissure. The third explanation, which is backed by the convincing post-mortem studies and experimental work on monkeys by Reid and Cone (1939), is that the nerve is stretched and compressed by the hippocampus which, as the intracranial pressure rises, herniates down through the tentorial opening. These workers also showed what a high extradural pressure was required in some animals to produce dilatation of the pupil—it may nearly equal the systolic blood pressure. This emphasizes the gravity of the sign and how if the pressure is not quickly relieved, infarction of the mid-brain may follow. I am sure that in the majority of cases this latter explanation is the correct one.

It is perhaps more important to observe that in nearly half the cases of this series there were no abnormal eye signs and it is apparent from the mechanism whereby they are produced that they should be regarded as late and inconstant signs.

*Pulse.*—Classically the pulse is slowed and in 10 cases it did fall below 60 per minute. A rapid pulse, however, is unusual save as a terminal event and in only two patients was it above 100 per minute.

#### *Ancillary Investigations*

*X-ray Skull.*—Fracture of the skull is common and indicates the site of the clot correctly. This investigation was carried out pre-operatively on 21 of the cases and a fracture, subsequently shown to be overlying the hæmatoma, was seen in 17.

That extradural hæmatoma may occur without fracture of the skull has been reported previously. There were four such examples in this series; two of these have been reported previously by Falconer and Schiller (1942) in a paper drawing attention to this point. All were temporal hæmatomas with tearing of the middle meningeal vessels.

In all, 25 cases showed fractures of the skull over the hæmatoma seen either on X-ray, at operation, or at autopsy. These were usually linear but three were comminuted depressed fractures and two showed multiple fissured fractures on the affected side extending to the base.

The position of a *calcified pineal body*, as seen in the antero-posterior as well as in lateral X-ray views, is very helpful in diagnosis. The pineal was seen in five of our cases; in three there was a marked shift away from the side of the lesion which was diagnostic in two of them, since there was no accompanying fracture of the skull. It is, however, important to note that a central pineal does not exclude a hæmatoma in sites other than temporal; one of the cerebellar and one of the sub-frontal cases of this series had a central pineal.

In one case a fracture into the middle ear with otorrhœa resulted in a spontaneous ventriculogram which showed a shift of the contralateral ventricle away from the side of the lesion. Ventriculography was only deliberately performed in one case. There was a marked shift of the ventricles to the right without any deformation of the frontal or temporal horns on the left side, and at operation subsequently a large left temporal hæmatoma was disclosed. Air studies are rarely required and actually dangerous. Direct exploration is always the method of choice and ventriculography is reserved for those cases where the evidence strongly suggests a clot but burr-hole exploration has proved negative. Whether angiography will prove a practical alternative in these cases remains to be seen.

*Cerebrospinal fluid.*—A pre-operative lumbar puncture was performed on 13 patients; in only eight was the spinal fluid pressure over 200 mm., five were within normal limits. The fluid was clear in five cases, blood-stained in eight—heavily so in one. Although these numbers are small, it is obvious that a clear fluid under increased pressure is by no means the rule and the spinal fluid findings are really little help in diagnosis. It is particularly important to realize that a normal or low lumbar and ventricular pressure may obtain in the presence of a large clot. Thus in one case in which a very large frontal extradural hæmatoma was missed at operation, the lumbar puncture pressure was 100 mm. and the ventricular pressure 60 mm.

These wide differences in pressure readings in the presence of a clot are difficult to explain. There has always been considerable doubt as to the validity of lumbar puncture pressure readings as a true indication of the intracranial state of affairs shortly after a head injury which, in the earlier stages, may be accompanied by shock and, later on, by dehydration (so common in the unconscious patient due to inadequate fluid intake). That these latter features are often responsible for low pressure readings is beyond question, yet they cannot be the only factors responsible for one has encountered cases with large intracranial space-occupying lesions where there was a normal or low spinal fluid pressure and no obvious cause such as shock, dehydration or evidence of internal herniation to account for it. It seems that the explanation must be sought in more subtle alterations of fluid interchange or in an interference with the normal secretion of cerebrospinal fluid.

In view of these findings, should a lumbar puncture be performed, for not only is the interpretation of the result equivocal, but in performing this examination valuable time may be lost; there is also the risk of precipitating a pressure cone in the presence of a space occupying lesion. As against this, if the pressure is known to be raised it is a useful guide to treatment; also the finding of a bloodstained fluid is evidence of an underlying cerebral contusion and this may be helpful not only in prognosis but, at operation, in determining whether the dura should be

opened to exclude a subdural hæmatoma, which, as will be seen later, is usually accompanied by bloodstained spinal fluid.

I think that where an extradural hæmatoma is suspected the risks of performing a lumbar puncture far outweigh the possible advantages, certainly if done within the first 24 hours following injury when speed in operation for the rapidly advancing compression is all important and the chance of a pressure cone highest.

### *Extradural Hæmatoma in Atypical Sites.*

In the majority of cases the hæmatoma is in the temporal fossa, the bleeding coming either from the main trunk of the middle meningeal artery, or, more commonly, from one of its branches. Thus 21 of the 29 acute cases were so situated and in all the 18 cases explored, a tear in the vessel wall or active bleeding from it was demonstrated.

The observations of Bell (1817) and Erichsen (1884) provide an adequate explanation of the mechanism whereby a comparatively small vessel can force blood between the dura and the bone to produce a massive hæmatoma and severe pressure. The initial blow tears the dura away from the bone and the torn vessel thus bleeds into a preformed cavity, the pressure against the dura being the product of the pressure in the artery and the capacity of the cavity. Against this pressure the dura readily strips from the bone so that the hæmatoma steadily enlarges. There are also important secondary effects to this process. It is common experience at operation that in addition to the main vessel, hæmorrhage may be very troublesome from numerous other radicles which not only add to the difficulties of the operation but may be a cause of recurrent clot later. The floor of the middle fossa is bound by venous sinuses, and bleeding from their numerous tributaries can be quite severe as the operation of trigeminal root section by the subtemporal route testifies. As an extradural clot expands, these radicles are torn and venous bleeding not only adds to the existing clot but in some cases indeed seems to be responsible for most of it. Further, the dura is congested as a result of the increasing intracranial pressure and the compression of the meningeal veins by the clot so that it may present at operation an oozing surface extremely difficult to control. Wood Jones (1912) drew attention to the part played by the middle meningeal veins in some cases of extradural hæmatoma and what it amounts to is that by the time an extradural hæmatoma comes to operation, both arterial and venous bleeding have contributed.

In 10 of these 34 cases, however, the clot was situated elsewhere, an incidence of 29 per cent.; six were in the anterior fossa, one confined to the parietal region, and three in the posterior fossa. It may be stated here that one of the main reasons for the high mortality of extradural hæmatoma is the presence of clots in these atypical sites. A frontal fracture may tear one of the anterior meningeal arteries and cause a hæmatoma in front or beneath the frontal lobe; the transverse or sagittal sinuses

may be torn by a traversing fracture and lead to a cerebellar or parietal clot; where there is a cerebral laceration with tearing of the overlying dura, clot may extrude through the opening and form an extradural mass; or the bleeding may come entirely from small dural vessels or from diploë in the bone.

These clots are difficult to diagnose and are easily missed at operation as will be illustrated later. Close attention to fracture lines and the presence of scalp marks are very helpful in localizing them and where a clot has not been found at the first exploration the case should always be reviewed with these two points in mind.

The diagnosis of extradural hæmatoma in the posterior fossa is particularly difficult. The three cases in this series will be reported elsewhere: briefly, they resulted from falls on the back of the head, fracture of the occiput was present and the lumbar C.S.F. was bloodstained and under high pressure. All three showed severe damage to the frontal lobes at autopsy which was not only a major factor in causing death but the explanation of the apparent false localizing signs which were present in two of them. It seems that an injury sufficient to produce a fracture of the posterior fossa and extradural bleeding often produces, by the rotational forces applied to the brain, severe cerebral contusion and hæmorrhage disruption particularly of the frontal lobes.

#### ACUTE SUBDURAL HÆMATOMA

*Definition.*—Some bleeding into the subdural space commonly accompanies the more severe head injuries where there is marked cerebral contusion and laceration, and at operation or autopsy it is seen as a thin film of blood diffusely distributed over the surface of the brain but clearly not compressing it. The cases described here as acute subdural hæmatoma are those in which the hæmatoma was sufficiently large to compress the brain and was at least 0.5 cm., and usually 1.0 cm. or more, in thickness; they were acute since they gave rise to symptoms in the early days following the injury, usually within the first 48 hours, but an upper limit of 14 days before operation or death was made. This apparently arbitrary division in the time between acute and chronic subdural hæmatoma is, in fact, in accord with clinical experience; for the earliest "chronic" cases usually come to operation some three weeks after injury and may in the interval have apparently recovered from the effects of the head injury, whereas the acute cases remain ill from the outset. The incidence of acute subdural hæmatoma in this series was just under 1 per cent.; other clinics have given much higher figures but this naturally varies with the interpretation of the term.

#### *Clinical Signs in 21 Cases*

Acute subdural hæmatoma may follow a trivial injury due to rupture of a cortical vein as it traverses the subdural space; in this case there is little or no brain damage. Bleeding from this source is usually slow, however, and more commonly results in the development of a chronic

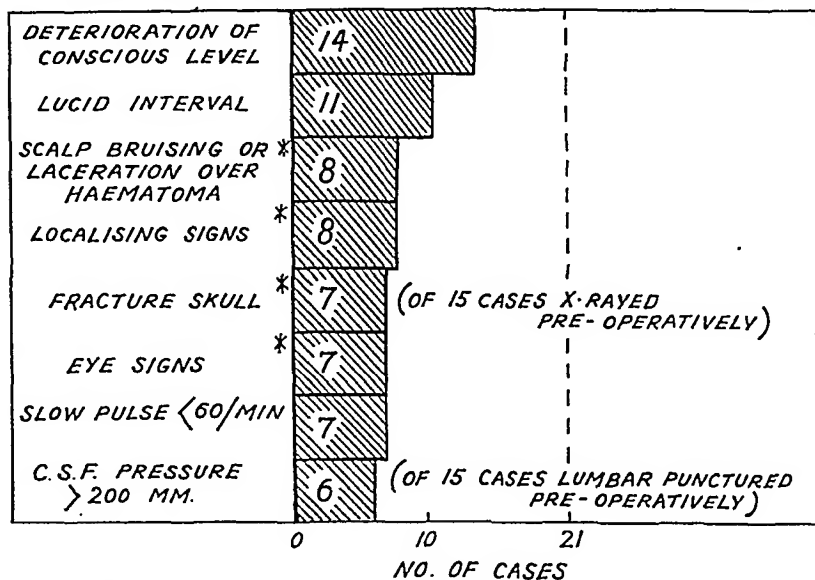
subdural hæmatoma. Acute subdural hæmatoma most frequently follows a severe head injury with marked cerebral contusion; cortical vessels are torn and blood enters the subdural space through tears in the overlying pia-arachnoid. Other cases may follow laceration of one of the great venous sinuses.

In this series 71 per cent. of the cases followed a car accident and none a local blow to the head. Again all the patients lost consciousness initially and in only nine of the 21 cases was this for less than an hour—findings which are in sharp contrast to those which obtain with extradural hæmatoma and reflect the graver head injury sustained.

The diagnosis is complicated by two factors: underlying cerebral contusion is usually present as well and its effects may dominate the clinical picture; and bleeding into the subdural space is frequently bilateral—the incidence was 29 per cent. in this series—and, as a result, localizing signs may be very misleading.

Reference to Table III shows that those localizing signs so reliable in lateralizing an extradural hæmatoma are unreliable in subdural hæmatoma. Thus a local scalp laceration or bruising on the side of the hæmatoma was present in eight cases but in as many cases again it was either a false

TABLE III  
SIGNS IN 21 CASES OF ACUTE SUBDURAL HÆMATOMA



\* Correctly indicating the site of the hæmatoma

localizing sign or was present on one side only in a bilateral hæmorrhage; whereas in 11 of the 21 cases there were unilateral long tract signs; in

three of these the hæmatoma was bilateral; and in three other cases the long tract signs were on the ipsi-lateral side. Eye signs were of diagnostic value in only seven of the 21 cases and in two cases the pupil on the side opposite to the hæmatoma was dilated.

### *Ancillary Investigations*

*X-ray Skull.*—Fracture of the skull is commonly present but may be misleading. Thus of 15 cases X-rayed pre-operatively a fracture was reported in 10; in seven this was on the side of the subdural clot but in three on the opposite side. Altogether a fracture was present in 16 of the 21 cases seen either on X-ray, at operation or at autopsy.

*Cerebrospinal Fluid.*—As in extradural hæmatoma, lumbar puncture pressure readings were of little help. In only six of the 15 cases punctured pre-operatively was the pressure above 200 mm. Thirteen yielded a bloodstained C.S.F. and the fluid in the other two was yellow although free from red cells. A high protein may be significant for in nine of the 11 cases where this was estimated the values found were far in excess of what could be accounted for by the amount of blood present; in six cases it was over 100 mgm. per cent., the highest figure being 250 mgm. per cent. in a fluid containing only 1,820 red blood cells per c.mm.

It is, therefore, apparent that one cannot be precise about the diagnosis before operation and there is no clinical picture characteristic of acute subdural hæmatoma. A lucid interval was present in 11 of these cases, and a provisional diagnosis of extradural hæmatoma was usually made. Otherwise the signs leading to exploration were deterioration in the level of consciousness; or the appearance of fresh signs in the central nervous system, such as a weakness of one side, or pupillary changes; or, as in two cases here, persisting long tract signs with onset later of papillædema.

## OPERATION

### *Extradural Hæmatoma*

I only wish to draw attention to a few points in the surgery of extradural hæmatoma, for the principle of burr hole exploration with subsequent enlargement if necessary is, I think, generally agreed by all as the method of choice. Bone flaps have little place in this urgent operation.

Where to explore? The common site for extradural hæmatoma is the temporal fossa, and in this event a burr hole in front of the ear will disclose the clot. But I would insist that to advocate, as has been done in the past, a routine practice of bitemporal burr holes is fallacious and will lead to several clots being missed. The correct place to explore initially is that indicated by the localizing signs, if present, the position of fracture lines and the site of scalp bruising or laceration. The whole head should be shaved in order to allow full inspection of the scalp and so that several burr holes can be made if required.

Twenty-six of the acute cases in this series were explored and in four the clot was not found ; two were subsequently shown to be cerebellar and two frontal. These frontal cases illustrate how easily even a large clot may be missed although the exploratory burr hole may lie less than 1 cm. from the edge of the clot for, in these circumstances, the brain is so tight that adequate exploration within the vicinity of the burr hole may prove impossible.

10518/43.—A woman, aged 37, fell off her bicycle. She was dazed only and went home. The next morning, however, she could not be roused and when seen at hospital some 20 hours after the injury she was stuporose, pupils unequal, slight left-sided weakness and bilateral upgoing toes. No fracture was seen on the X-ray. There was bruising around the right eye. She was immediately taken to the theatre and bitemporal and right frontal burr holes made ; the brain was very tight everywhere, but there was no extradural or subdural clot seen. She died early next morning.

The autopsy showed a massive spherical hæmatoma mainly beneath the right frontal lobe measuring  $8 \times 6 \times 5$  cm. (Fig. 1) and reaching to within 0.8 cm. of the frontal burr hole and 1.2 cm. of the right temporal burr hole. There was a fissured fracture in the right anterior fossa running from the posterior end of the cribriform plate across the floor of the fossa and crossing four anteriorly directed grooves in the bone for the meningeal vessels, which were presumably the source of the bleeding. The right frontal lobe was severely flattened, there was tonsillar and tentorial herniation, and bruising of the left temporal lobe.

It may be emphasized again that of the 29 acute extradural hæmatomas in this series no less than eight were in sites other than temporal, and all could be accurately localized by attention to the site of fracture, scalp marks and localizing signs.

Bilateral extradural hæmatomas are reported, but are rare ; none was encountered in this series. If, therefore, the clot is found at the first exploration, and it adequately explains the signs present, then I do not think it is necessary to explore the other side as a routine, though there should be no hesitation in doing so if there is any doubt.

Whether to open the dura is a debatable point. Post-operative cerebral œdema has always been quoted as a frequent complication after operation and for this reason some surgeons have advised opening the dura widely to act as a decompression. I could not find in this series any evidence that œdema was a common complication unless there was already severe cerebral damage present. The dura was not opened in this series as a routine, and I do not think it is necessary in the uncomplicated case. An exploratory opening in the dura is a different matter however. A dura which is discoloured or which bulges after evacuation of the clot must be opened ; but the appearance of the dura is naturally dependent on its thickness and a subdural collection of blood or cerebrospinal fluid may exist beneath a perfectly normal-looking dura. For this reason there is everything to be said for a small exploratory opening in all cases. This should certainly be done where there

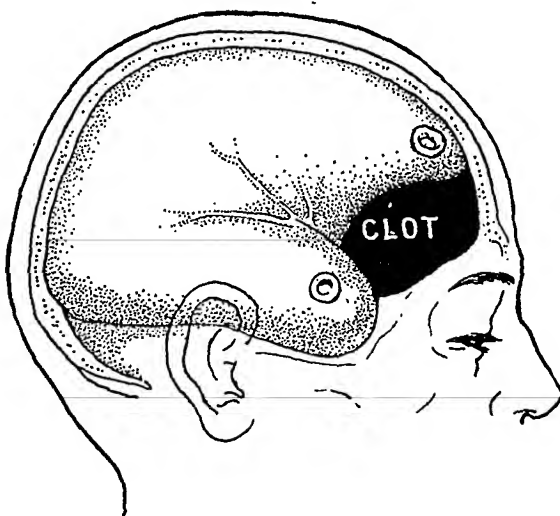


Fig. 1.

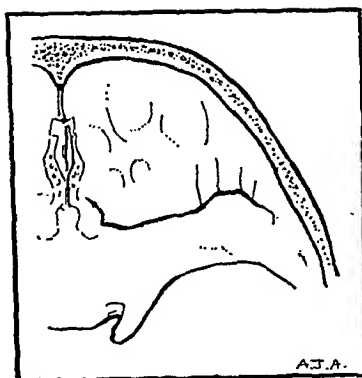


Fig. 1 (Diagram).

Fig. 1. (Case 10518/43.) Right sub-frontal extradural clot missed at operation. Note the temporal burr hole which was situated 1·2 cm. from the edge of the clot and the frontal burr hole 0·8 cm. away. The fracture in the anterior fossa, seen at autopsy, is shown in the accompanying diagram.

is clinical evidence of underlying pathology as judged by an initial period of unconsciousness of an hour or more, or the presence of blood in the C.S.F.

Should one insert a drain? This was done in about half the cases of this series. If after evacuation of the clot the dura is dry and comes up flush with the bony defect, it is probably of little consequence, but it is wise to drain for 48 hours in those cases where there has been considerable



oozing from the dura and where the dura has not come up so that a dead space remains between it and the bone.

It is axiomatic that once an extradural hæmatoma is diagnosed, operation should be immediate and the urgency has been repeatedly stressed in the past. It can hardly be over-emphasized. Where the history and signs indicate a rapidly advancing hæmatoma and localization is clear, valuable time should not be lost in performing radiography and lumbar puncture. Six patients in this series were taken straight to the theatre from the admission room; all had large clots and four of them made a good recovery; the other two died on the table, despite immediate exploration.

13706/42.—A woman, aged 46 years, was knocked off her bicycle. She was only momentarily unconscious, and when seen by her doctor three hours later was diagnosed as having mild concussion; the central nervous system was otherwise normal. The patient became unconscious two-and-a-half hours later. She was admitted to hospital nine hours after the accident and by then was deeply comatose. She was taken straight to the theatre and the right temporal fossa explored. No anæsthetic was required. A large clot was found, but the patient died whilst this was being evacuated.

At autopsy there was a massive clot,  $10 \times 13 \times 2$  cm., in the temporal fossa; the brain was congested and flattened, but there was no gross cerebral damage.

These patients require constant supervision from the time they are admitted, for deterioration may be quite sudden. For this reason, if an X-ray is requested, the radiologist should always be warned of the nature of the case before sending the patient for examination. The following case illustrates how close observation can lead to a timely intervention.

52840/46.—A man of 32 years was hit over the right eye by the tail of an aeroplane which was taxi-ing along the runway. He was unconscious for 30 minutes and then, after a short lucid interval, relapsed. When seen two-and-three-quarter hours after the accident he responded to painful stimuli only. The right eye was swollen, but both pupils were normal in size and reacted briskly to light. There was a left hemiparesis.

He was sent for X-ray examination, and 20 minutes later it was noticed in that department that the right pupil was now dilated and fixed to light. Exploration was carried out immediately, and a large clot, filling the whole of the right anterior fossa and part of the middle fossa, evacuated. The patient made a good recovery.

### *Acute Subdural Hæmatoma*

In practice one finds that where there has been a definite lucid interval, a provisional diagnosis of extradural hæmatoma has probably been made and one proceeds accordingly. Where there are no localising signs or where a heavily bloodstained spinal C.S.F. has suggested a diagnosis of subdural hæmatoma a parietal burr hole is made. Further, since subdural hæmatoma is frequently bilateral, both sides should be

explored. A blueish tense appearance of the dura suggests an underlying hæmatoma and, on opening the dura, either fluid blood escapes under pressure or clots begin to extrude through the dural opening.

It is not customary to find the bleeding point in these cases for the bleeding, whether from a cortical vein, a venous sinus, or from a cerebral laceration, has usually stopped by the time operation is performed. In only one of the 17 cases operated on was a definite bleeding point—a small cortical artery—found.

The evacuation of the fluid chronic subdural hæmatoma is usually a simple procedure but the treatment of the acute hæmatoma may be technically very difficult for two reasons; the hæmatoma may be partly or wholly solid; and underlying brain damage is commonly present and in some cases a definite intracerebral hæmatoma has formed which will also require treatment in addition to the superficial collection, if pressure is to be adequately relieved. One has therefore to discuss the treatment of acute subdural hæmatoma when (1) the hæmatoma is mainly fluid, (2) it is mainly solid, (3) after evacuation of the hæmatoma the cortex bulges through the dural opening indicating that the pressure is unrelieved.

(1) *The Hæmatoma is mainly fluid (10 cases).*—Fortunately this is the commonest state of affairs and on opening the dura the blood readily escapes. These circumstances make accurate measurement of the amount of blood present impossible; on an average 30-80 c.cms. are collected. Small clots also escape along with the fluid blood. By gently depressing the cortex with a small spatula, further blood wells up and may be sucked out.

These hæmatomas are distributed over the hemisphere fairly uniformly though, due to gravity, larger collections may be found over the cerebral poles. Two suitably placed burr holes will usually be effective in evacuating the hæmatoma, but one should not be content with a single burr hole as this may result in leaving behind a considerable part of the hæmatoma. This was the cause of death in one of our cases. A second burr hole is therefore made on the same side, e.g., frontal if the first exploration was parietal, and the subdural cavity irrigated with warm Ringer's solution until the washings are clear. In this way the hæmatoma is completely drained. At the end of this procedure the cortex is usually shrunk away from the dura by some 1-2 cm., but, in favourable cases, begins to expand immediately to obliterate the dead space. In these circumstances no drain is inserted as one fears the attendant risk of forming a track for infection and indeed it is mechanically impossible to drain the subdural space adequately. As an alternative, the dura is left widely open for the width of the bony opening and the subgaleal space around opened up by undermining the scalp incision with a knife so that any further blood may readily escape into this space and be absorbed. The wound is then closed in layers. This method has been found

to be quite effective and superior to attempting drainage of the subdural space by tubes.

(2) *The Hæmatoma is mainly solid (3 cases)*—Much less commonly the hæmatoma is solid or partly so. In some cases it may still be possible by enlarging burr holes, and with suction and irrigation, to remove it satisfactorily; otherwise an osteoplastic flap will have to be turned.

(3) *There is brain swelling (4 cases)*—A major operative problem is encountered when, after removal of the subdural hæmatoma, the cortex, sometimes obviously contused and œdematous, bulges through the dural opening. It is true that the subdural hæmatoma in many of these cases plays only a relatively small part in a clinical picture produced mainly by cerebral contusion and laceration and the signs which led to exploration herald the termination of what is essentially a fatal injury. Yet this is by no means always so and there are three other factors to consider.

(a) *The brain swelling may be quite localised* and by preventing drainage of the hæmatoma lead the operator to suppose that the subdural collection has been completely evacuated whereas a considerable part of it may have been thus loculated off. This is a further point in favour of performing at least two burr holes on the side of the hæmatoma.

(b) *An extradural or subdural hæmatoma may exist elsewhere*, perhaps on the opposite side, and this is responsible for the bulging cortex. The case must therefore be reviewed from this aspect.

(c) *An intracerebral clot may be present*, which, together with the surrounding œdema, forms a space-occupying lesion.

In this series there were five cases of a subdural hæmatoma combined with an intracerebral hæmatoma and, if to these are added the four cases of intracerebral hæmatoma mentioned earlier where there was a negative exploration for a surface hæmatoma, and the one in association with an extradural hæmatoma, we have 10 cases of intracerebral hæmatoma in the total series of 91, an incidence of 11 per cent. All but one were situated in the frontal or temporal lobes; two lay within the Sylvian fissure and presumably resulted from rupture of one of the middle cerebral group of vessels or possibly an aneurysm, although this could not be demonstrated; three were seen on the surface of the cortex, of which one had burst through the frontal pole over a diameter of one inch to form in addition a mass of sub-arachnoid clot (Fig. 2); four were within the white matter and were not disclosed until the brain was sectioned, although the surface cortex was swollen and either pale or congested. The remaining one was in the mid-brain. Their average diameter was two inches. All the patients showed deterioration of the conscious level and in six there was a definite lucid interval. It is perhaps surprising to find that a lucid interval was so commonly present in intracerebral hæmatoma and on these small numbers

one cannot be dogmatic. But it does suggest that the bleeding does not always necessarily occur at the time of injury but may come on some hours later, secondary perhaps to damage to vessel walls consequent on the injury.

The rupture of an abnormal vessel or aneurysm is always a possible cause for the bleeding, particularly in those cases which follow a mild injury or have a long lucid interval, but no such cause was found in these cases; moreover, the lesion is not restricted to the older age groups with cerebro-vascular disease for four of these ten patients were under 35 years of age. Of the seven cases which came to autopsy in only one was gross cerebral contusion or laceration present elsewhere in addition to the hæmatoma. The facts most relevant to our argument are that not only may these intracerebral hæmatomas accompany a subdural hæmatoma but their clinical picture may mimic a surface hæmatoma even to the production of a lucid interval and that they may occur as an essentially remedial localised lesion in the brain.

Where, therefore, after evacuation of a subdural hæmatoma, the brain remains tight and cortical clot can be seen through the burr hole, its removal by suction after enlarging the bony opening would seem a logical step. That this more radical treatment can be attended by success is illustrated by the recovery of the three patients in this series on whom it was performed.



Fig. 2. (Case 43907/45.) Intracerebral clot  $4 \times 4 \times 4$  cm. in the left frontal lobe which had burst through to the surface to produce a sub-arachnoid hæmorrhage. The left ventricle was flattened and there was bilateral tentorial herniation. The patient, aged 61 years, was initially unconscious for a few minutes only and thereafter lucid for nearly 24 hours.

49022/45.—This man, aged 53 years, fell off his motor-cycle. He was knocked unconscious, and on his way to hospital had a fit. He improved, and by the third day was cooperative though still confused. The lumbar puncture pressure was 130 mm. and the C.S.F. bloodstained. On the seventh day he developed a slight left hemiparesis. Over the next few days his conscious level varied, but on the 11th day his pulse slowed, he became more drowsy and finally he responded only to painful stimuli.

At operation 11 days after the accident, about 20 ccs. of subdural clot were evacuated from the right side through frontal and parietal burr holes. The left side was normal, and the ventricle on this side was tapped and the pressure found to be atmospheric. As, however, the cortex was bulging through the dura on the right side it was felt that further clot must exist elsewhere; accordingly a right temporal burr hole was made. On opening the dura and subsequently enlarging the bony opening, a large clot 4 cm. in diameter was found in the temporal lobe. This was sucked out and hæmostasis secured by placing muscle stamps in the cavity. The subdural space could then be irrigated freely and further surface clot was evacuated.

His post-operative course was complicated by a low pressure state, but ultimately the patient made a good recovery.

Where an intracerebral clot does not present at the surface, routine exploratory needling is liable to be both dangerous and ineffective—dangerous because it may create more damage and resultant œdema, ineffective because the hæmatoma is rarely sufficiently fluid to allow easy aspiration without blocking the needle. However, it is justifiable to do this where the clinical picture indicates a lesion in a particular site or where the appearance of the cortex suggests an intracerebral mass beneath; if clot is found it is usually better to enlarge the exploratory opening and evacuate it through a formal cortical incision.

(d) *When the brain remains tight* after evacuating the hæmatoma, and no cause for this such as outlined above can be found, should one do more, for clearly the pressure is unrelieved? In these cases the underlying cerebral contusion is the main cause of the symptoms which led to exploration, and to answer the question we must refer to the findings in the 19 cases of cerebral contusion mentioned earlier which were explored for a surface hæmatoma, with negative results.

Of these, 11 showed evidence of raised intracranial pressure either pre-operatively from the lumbar puncture findings or at operation by the brain bulging through the dural opening or escape of subdural blood under pressure. Nine of these 11 cases had a thin film of subdural blood over the hemisphere so that they are comparable with the cases under discussion, differing only in the amount of subdural blood present. All save one proved fatal and at autopsy severe contusion or laceration of the frontal or temporal lobes, commonly the latter, was present. One cerebral pole might be disrupted, the resultant mass of disintegrated brain and clot with local œdema forming a space-occupying lesion. Internal herniation of the brain at the tentorium or the foramen magnum was common and clearly pressure was an important factor in the fatal

termination. Moreover the autopsy findings confirmed that the localising signs present in nine of the 11 cases—a dilated pupil or a hemiparesis—were reliable and had accurately indicated the side of the main cerebral damage.

In the other eight cases there was no evidence of increased intracranial pressure. Subdural blood was present in only two of them. Three of the patients recovered.

It must be stressed that these cases of severe cerebral contusion are not primarily surgical problems and many are essentially fatal injuries; but if the patient has survived the early hours after the injury, particularly the first 24 hours, this is too ready an assumption. These findings suggest that where the march of events has led to exploration and there is evidence of raised intracranial pressure, then if this can be relieved some of these patients might be saved. In selected cases therefore, and particularly where the pressure has been only partly relieved by evacuation of a subdural hæmatoma, there is much to be said for a subtemporal decompression or in some a frontal bone flap on the side indicated by the clinical signs. Damaged brain and clot may be removed and a decompression provided.

### POST-OPERATIVE COURSE

It is interesting to observe that even those patients who make a straightforward recovery after evacuation of a surface hæmatoma do not, as a rule, regain full consciousness rapidly. This would be anticipated in the majority of the cases of subdural hæmatoma where there is underlying cerebral contusion, but it also obtains in extradural hæmatoma. Thus, of 10 such cases in this series, although all showed some improvement immediately following operation, only five had recovered full consciousness within 24 hours after operation, the others remaining confused and drowsy and making a much slower recovery over the next five days or so. Moreover, this slower rate of recovery could not be ascribed to the effects of any more severe brain damage over that sustained by the first group as judged by the duration of the initial unconsciousness, nor could it be related to the differing time intervals between the accident and operation.

This slow clinical recovery is reflected in the encephalographic findings of one such patient, where a four-day-old temporo-parietal extradural hæmatoma had been evacuated. The duration of the initial unconsciousness was only 15 minutes. Sixteen days after operation the X-rays showed that there was still a considerable shift of the ventricles to the opposite side. (Figs. 3, 4.) The decompression was slack. This suggests that not only does the brain take time to recover from the effects of compression, but that displacement may persist for some time after operation.

Failure to show some improvement after operation, however, should always raise the suspicion of a recurrent clot or a hitherto undiagnosed clot elsewhere.

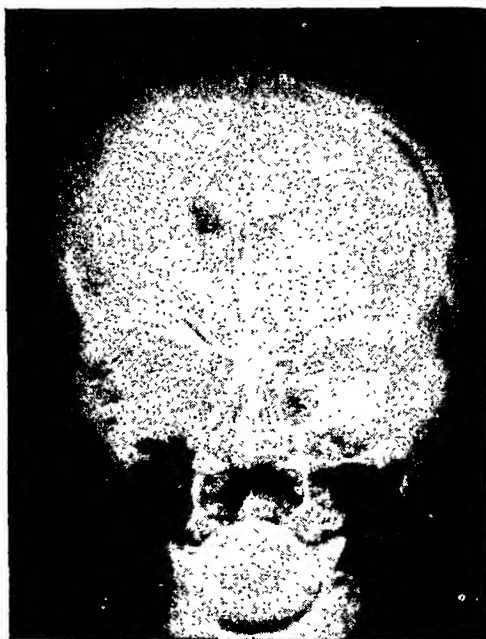


Fig. 3.

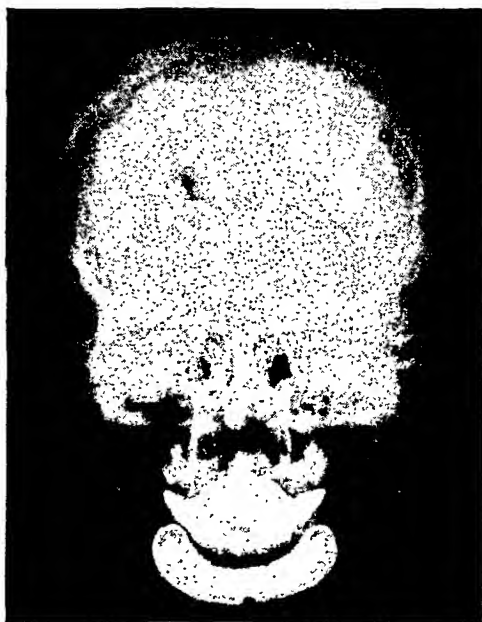


Fig. 4.

Figs. 3 and 4. (Case M.R.C. 2044.) Encephalogram 16 days after evacuation of a left temporo-parietal extradural hæmatoma. The decompression was slack. Note that the ventricular system still shows a shift to the right.

Motor signs which had developed along with the signs of cerebral compression showed immediate improvement and gradually disappeared over the following two or three weeks. A dilated pupil frequently came down immediately after operation, although some inequality might be distinguishable for a few days.

The main complications which develop are recurrent bleeding, "low pressure state" and cerebral œdema.

*Recurrent bleeding.*—In extradural hæmatoma this may arise from the divided ends of one of the main meningeal branches, but it is, perhaps, more common to find at re-exploration no one definite bleeding point but oozing from multiple points in a very vascular dura. This is particularly so where intervention has been late, and the clot has already partly organized. This latter type can be difficult to deal with and time-consuming. Three cases of extradural hæmatoma in this series were re-explored for recurrent clot; in one the bleeding was from a meningeal branch, in one from a congested dura, and in one, which will be described in the section on œdema below, from a brain laceration where at the first operation the dura had been left open.

71215/47.—Right temporal extradural hæmatoma evacuated eight hours after the accident; at the operation the middle meningeal artery was found severed and was coagulated.

Following operation the patient improved and responded to his name, but three hours later relapsed, became unresponsive and developed Cheyne-Stokes respiration. He was returned to the theatre and the wound reopened. More clot was present, and after removal it was seen that the proximal end of the middle meningeal artery was bleeding. This was again coagulated and the wound closed. Thereafter the patient made a rapid recovery.

The importance of recognizing this complication early is emphasized by the following case, which ended fatally. Here the signs of cerebral compression were minimized by the fact that a partial decompression was afforded by a profuse cerebrospinal fluid otorrhœa. The clot was not evacuated until the sixth day; presumably by then the prolonged compression had resulted in irreversible changes.

70102/47.—This man, aged 46 years, fell out of a tree and was unconscious for some minutes. He recovered, but six hours later became drowsy, the pulse fell to 44/min., and he developed a right hemiplegia. An X-ray prior to operation showed multiple fissured fractures on the left side and the right ventricle spontaneously filled with air (there being a communication between the ventricular system and the left middle ear) and displaced to the right. At operation, eight hours after injury, a large left extradural hæmatoma extending over the hemisphere was evacuated; the main bleeding was seen to be coming from a torn anterior branch of the middle meningeal artery. The wound was closed without drainage.

The patient did not improve after operation. A needle was introduced daily for the next two days through the wound into the extradural space and



15-20 cc. blood withdrawn. Cerebrospinal fluid discharged profusely from the left ear. It was thought that his mental state was due to cerebral contusion, but on the sixth day after operation the patient had a short attack of Cheyne-Stokes respiration, and his blood pressure rose to 190/128; a lumbar puncture yielded bloodstained fluid under a pressure of 170 mm. Thereafter he responded less to painful stimuli. The wound was, therefore, reopened, and a large extradural clot was disclosed. The bleeding seemed to be coming from high up near the sagittal sinus so that a small bone flap was turned down and the bleeding from the dura arrested by muscle stamps and by stitching the dura to the temporal muscle; a drain was left in. The patient's condition remained unchanged and he died two days later.

At autopsy there was a small amount of extradural clot in the region of the skull defect to a depth of 0.5 cm.; the brain was flattened over an area 10×9 cm., and there was marked cerebellar herniation. Apart from a few areas of softening in the left temporal pole and a contused area measuring 2.5 cm. in the right temporal pole, the brain appeared normal.

A clot is especially prone to form where, after the first operation, the brain does not expand readily to obliterate the space between the bone and dura, or in subdural hæmatoma between the brain and dura. It has been mentioned previously that when this happens with extradural hæmatoma one should always leave in a drain and it may be wise also to stitch up the dura to the temporalis muscle.

A dead space is commonly left after evacuating a chronic subdural hæmatoma; in order to obliterate it these patients are nursed with the foot of the bed on high blocks and abundant fluids given. The disappearance of the air in the subdural space as the brain expands may be followed by serial X-rays in the brow-up lateral position. Fortunately, in acute subdural hæmatoma the brain usually comes up readily and in only one of our cases was there a post-operative relapse due to re-accumulation of blood which had to be drained. One should be careful, however, in nursing the acute subdural case with the head down for, if the source of the bleeding has been venous, the resulting increased venous pressure may well begin it afresh, an event which is very unlikely in the chronic variety. I treated one case of acute subdural hæmatoma on these lines and there was recurrent bleeding from which the patient died. At autopsy the cause of the hæmorrhage was a tear in the transverse sinus and I have no doubt that the reduction of pressure after evacuation of the clot, followed by nursing in the head down position to obliterate the subdural space, was sufficient to cause fresh bleeding. Therefore I do not think that the post-operative regime suitable for chronic subdural hæmatoma should be applied as a routine to the acute case unless a definite low pressure state develops (q.v.).

“*Low pressure state.*”—Neurosurgeons are familiar with this state of affairs which, from time to time, follows head injuries and intracranial operations. The patient becomes stuporose and this is accompanied by a very low intracranial pressure—a decompression will be seen to be markedly indrawn and the lumbar cerebrospinal fluid pressure about

atmospheric ; improvement follows the administration of abundant fluids and raising the foot of the bed. The mechanism of the condition is not well understood. Several of these patients are dehydrated and although correction of the fluid balance is followed by improvement, the level of consciousness does not always lighten parallel with this, although severe dehydration will certainly prolong the coma and may indeed precipitate the condition. Nor is it exclusively related to the cerebrospinal hypotension for in many other conditions such a low intracranial pressure obtains without impairment of consciousness. There is some evidence to suggest that the essential lesion is in the brain stem, probably the hypothalamus, and that with surface hæmatomas, distortion by the pressure of the clot is the main factor.

The clinical picture may closely resemble that of a recurrent clot but there are no lateralising signs. Two such cases occurred in this series ; one followed the evacuation of a subdural hæmatoma where dehydration was clearly a major factor, and one after removal of an extradural hæmatoma where there was no evidence of any marked dehydration.

49022/45.—The pre-operative and operative details of this case of subdural hæmatoma with intracerebral clot have already been described (page 258).

Following operation the patient's condition was critical due to an exacerbation of his chest condition. His respirations were very irregular and mucus collected to a degree which demanded almost constant aspiration. Bronchoscopy was performed on the second post-operative day and mucus aspirated from the left bronchus. Following this procedure the patient was much improved and the respirations became regular.

His mental state, however, had improved only a little following operation. On the day following operation the spinal pressure was 20 mm. with C.S.F. protein 30 mgms. per cent. On the fourth post-operative day the level of consciousness was worse and both lumbar and ventricular punctures showed a pressure of zero.

For the next seven days his lumbar puncture pressure remained atmospheric, with C.S.F. protein 80-120 mgms. per cent. He was given three pints of fluid daily by oral tube, together with intravenous glucose saline in the early stages ; the foot of the bed was raised. On five occasions an attempt was made to raise the intracranial pressure by intrathecal and intraventricular injections of air and saline. These made no difference to his mental state, and it is interesting that on one occasion after the intrathecal injection of 50 cc. air to leave a final pressure of 200 mm., a puncture two-and-a-quarter hours later showed a pressure of 10 mm. After a week the C.S.F. pressure rose to levels between 60-126 mm. but there was no improvement in the conscious level. During this period the blood urea was raised to 78-112 mgm. per cent. on the three occasions it was done and very significant was the fact that the C.S.F. chlorides were consistently at 800-880 mgm. per cent. on seven occasions.

It was not until the 24th day after operation that definite improvement began ; then the blood urea and C.S.F. chlorides had fallen to normal, and the lumbar C.S.F. pressure was 90 mm. with protein 30 mgm. per cent.

This case demonstrates very well the lack of direct correlation between the C.S.F. pressure and the mental state. Undoubtedly the water depletion

from which the patient was suffering prolonged his coma and in view of the blood chemistry it is clear in retrospect that although he seemed to be receiving reasonable amounts of fluid it was not enough—his depletion was gross and he required a very large amount of fluid to restore his fluid balance.

16859/43.—In this case a young, healthy woman of 36 years was operated on for an extradural hæmatoma 36 hours after injury. Before operation she was reasonably alert and cooperative, though aphasic, and although she had vomited twice during this period and we have no actual records of fluid intake, there was certainly no obvious dehydration present. At operation a massive extradural hæmatoma 11 cm. in diameter was found. There was a small underlying dural tear, 2.5 cm. long, with superficial abrading of the cortex beneath, but elsewhere the brain looked normal. The most striking feature was that after removal of the clot the brain remained shrunken away from the dura and did not expand at all. The dura was closed. She received a small quantity of intravenous saline as a vehicle for 2G pentothal required for sewing up the wound, and one pint of blood.

Whereas before the operation the patient was alert, following operation she was very drowsy and at first this was thought to be due mainly to the pentothal. Twelve hours after operation, however, she went into status epilepticus. The decompression was markedly indrawn. A low pressure state was diagnosed, and this was treated by intravenous saline and blocks to the foot of the bed. She made a slow improvement, but it was not until the third day that the decompression became flush with the skull. The patient regained consciousness by the fourth day and finally made an excellent recovery.

Patients in coma after head injuries are very liable to become dehydrated and their fluid balance requires careful supervision. In most cases it is a pure water depletion so that one should be warned against the over-administration of intravenous saline which may aggravate the condition one is trying to relieve. (Marriott 1947.)

*Cerebral Œdema.*—Although œdema is often quoted as a complication to be feared after these operations, no case was encountered in this series, where it developed in the absence of marked cerebral contusion and laceration. Even in the subdural cases only two showed marked generalized cerebral œdema at autopsy.

It is more important, however, to comment on the absence of œdema in cases of extradural hæmatoma since it is on account of the potential risk of œdema in the temporal region that some surgeons advocate opening the dura as a routine. Only two of the extradural cases showed at autopsy internal herniation either at the tentorial opening or the foramen magnum in the absence of extradural clot and both had marked cerebral contusion; one, a cerebellar case had contusion of both frontal lobes and the other, a temporal hæmatoma with an intracerebral clot, is recorded below. In this latter case death was due to œdema of the temporal lobe spreading

to the mid-brain which was more the result of the brain damage than of the overlying extradural clot.

HN 6518.—This patient, aged 27 years, fell off his bicycle and was admitted to hospital unconscious and bleeding from his right ear. He had a mild right hemiparesis. After improvement over the next few days, his headache became worse, and eight days after the accident the right leg was definitely weaker than before. Operation was performed. A small bone flap was turned down on the left side after a parietal burr hole had been negative and a temporal burr hole had revealed just the edge of a basal clot. The dura was very adherent to the bone, and this was thought to account for the fact that the clot which measured  $7.5 \times 2.5 \times 2.5$  cms. was confined to the area of the temporal lobe. A tear in the middle meningeal artery was seen on the floor of the middle fossa and the adjacent dura was also torn. The dura over the temporal lobe was tight, and therefore opened. One temporal convolution showed a marked blueish area, and on passing a needle into the brain through this area a large clot was encountered. The cortex was incised and 45 cc. of blood and clot were evacuated. The wound was then closed, the dura being left open.

Following this operation the patient remained deeply unconscious, and the next day he developed epileptic movements in the right arm. The wound was re-opened, and a large extradural clot, which was thought to have come from further intracerebral bleeding, evacuated. Part of the temporal lobe was removed to gain adequate exposure. Finally, the uncus, which was herniated down into the tentorial hiatus, was replaced with the aid of a brain retractor. At the end of this operation he was responding well, but seven hours later he again deteriorated. In spite of intravenous sucrose his condition became worse and the wound was reopened nine hours after the previous operation. There was no fresh clot, but the uncus was again engaged in the tentorial hiatus and was replaced. His conscious level improved after this re-exploration, but the next day he relapsed and despite ventricular tapplings and hypertonic injections he died, 12 days after the accident.

At autopsy the left temporal lobe was considerably swollen, with marked herniation of the left hippocampus, and a little of the right uncus. There was considerable lateral compression of the mid-brain with a recent hæmorrhage beneath the aqueduct  $0.8 \times 0.3$  cm. No significant extradural clot was present; bronchopneumonia.

This case illustrates the grave results of spreading œdema in the temporal region; the uncus becomes tightly impacted in the tentorial opening, the mid-brain is compressed and displaced with development of small hæmorrhages in its substance as a result of venous congestion. In such cases disimpaction by lifting the uncus out of the hiatus has been practised previously (LeBeau 1943) and indeed was performed twice in this case.

The conclusion one reaches on the frequency of cerebral œdema is that whereas local œdema around damaged brain is common and adds to the effect of pressure, generalized œdema is uncommon in these cases and, in the absence of cerebral damage, does not occur in extradural or subdural hæmatoma. It is possible of course that the slow recovery of some of the cases of extradural hæmatoma already referred to and the transient

setbacks which may occur in both types of hæmatoma during the post-operative period are due to vascular changes with local œdema.

### THE MORTALITY RATE AND ITS MAIN CAUSES

With one exception, an autopsy was performed on the 28 fatal cases in the series and the cause of death based on these findings and the clinical course is summarized in Tables IV and V. It will be seen that the majority of the deaths in the cases of acute extradural hæmatoma could be ascribed directly to the hæmatoma whereas cerebral contusion was the main factor in acute subdural hæmatoma.

#### *Acute Extradural Hæmatoma*

Fifteen of the 29 cases proved fatal, a mortality of 52 per cent. The cause of death in nine of these was the direct result of the hæmatoma (Table IV).

*Cases Undiagnosed (2 cases).*—Both these patients remained in deep coma from the time of the accident and died within 14 hours. Bleeding must take place very rapidly in this type of case and will always be extremely difficult to diagnose.

One had severe fractures of the leg together with lacerations of the scalp and hand; he was operated upon within one hour of the injury, the fractures reduced and splinted, and the wounds sutured. At the end of the operation it was noted that his pupils had become unequal but his condition by then was so poor that further intervention was not possible. One is naturally anxious to treat fractures as quickly as possible but it is wiser, in patients who also have a head injury, particularly those who are still unconscious, to defer definitive treatment whenever possible until one is more certain of the cerebral condition. In such cases I think there is everything to gain by observation for the first 12 hours with simple splinting of fractures in the bed, and chemotherapy if required.

Fig. (5) illustrates the typical autopsy finding in an undiagnosed case.

*Late Intervention (4 cases).*—Patients vary widely in their capacity to withstand cerebral compression and probably its rate of development is more lethal than the actual degree. A third factor is the duration of the compression for, if prolonged, the changes caused may be irreversible. Thus two patients were operated on immediately after admission to hospital, one nine hours and the other 13 hours, after the accident but both died on the table due to the rapidly developing compression; at autopsy there was a massive extradural hæmatoma with marked flattening of the brain and although there was a little cerebral contusion in each case the cause of death was clearly the acute compression. In the third case, although the signs indicated an extradural hæmatoma, their significance was not appreciated and attention was distracted by the presence of a broken leg. The patient was sent to the ward but over the next hour and a half rapidly deteriorated and at the end of that time artificial respiration was required. The extradural clot was removed at operation in the ward but the patient did not recover. Autopsy

# HÆMATOMA IN CLOSED HEAD INJURIES

TABLE IV

CAUSE OF DEATH IN ACUTE EXTRADURAL HÆMATOMA 15 CASES

Cause		Total
A. EXTRADURAL HÆMATOMA—		
1 UNDIAGNOSED .. .. .	2	
2 LATE INTERVENTION.. .. .	4	
3 NOT FOUND AT OPERATION .. .. .	3	9
B. CEREBRAL CONTUSION—		"
1 WITH HÆMATOMA ADEQUATELY TREATED .. .. .	3	
2 WITH SMALL UNTREATED HÆMATOMA .. .. .	1	4
C. OTHER CAUSES—		
1 MENINGITIS, WITH SMALL UNTREATED HÆMATOMA .. .. .	1	
2 SHOCK FROM SEVERE CHEST INJURY. EXTRADURAL CLOT EVACUATED	1	2
		15

TABLE V

CAUSE OF DEATH IN ACUTE SUBDURAL HÆMATOMA 13 CASES

Cause		Total
A. SUBDURAL HÆMATOMA—		
1 UNDIAGNOSED .. .. .	1	
2 INCOMPLETE EVACUATION OF CLOT	1	2
B. CEREBRAL CONTUSION—		
1 MARKED CONTUSION AND LACERATION .. .. .	4	
2 INTRACEREBRAL HÆMATOMA .. .. .	2	
3 CONGESTION AND ŒDEMA .. .. .	2	8
C. OTHER CAUSES—		
1 RUPTURE OF LIVER .. .. .	1	
2 BRONCHOPNEUMONIA .. .. .	1	
3 ? ACUTE PULMONARY ŒDEMA .. .. .	1	3
		13



Fig. 5. Autopsy findings in an undiagnosed case of temporal extradural hæmatoma. Note the typical shape of the clot, the flattening of the brain, and the displacement of the ventricular system.

showed only a little bruising of the opposite temporal pole. The fourth patient had recurrent bleeding after evacuation of the hæmatoma but was not explored again until six days later. The patient did not improve after this second operation and died two days later; at autopsy there

was no further clot or gross cerebral contusion but there was local flattening of the brain and marked cerebellar herniation. Death was presumably consequent on the prolonged compression of the brain by clot.

*Not Found at Operation (3 cases).*—These were all clots in atypical sites and their importance has already been mentioned. It stresses the fact that the routine practice of bitemporal burr holes is not applicable to all cases. All three had large hæmatomas at autopsy; one was cerebellar, one beneath the frontal lobe, and one anterior to the frontal lobe.

*Cerebral Contusion (4 cases).*—In these cases there was severe cerebral contusion which was considered the main cause of death; in three the extradural hæmatoma (two temporal, one cerebellar) had been successfully dealt with and in the fourth case, although a small cerebellar extradural hæmatoma had been missed, it was clear that the gross damage to both frontal lobes and the underlying cerebellar lobe was the main cause of death which may have been precipitated by lumbar puncture.

One would, of course, expect to find among the fatal cases of extradural hæmatoma those where there was accompanying severe cerebral contusion but the experience that the type of injury which results in an extradural hæmatoma is not of the severity to cause gross cerebral contusion is exemplified by a study of these fatal cases. Although 13 of the 15 showed some cerebral contusion or laceration, in seven it was limited to local bruising of one temporal lobe either on the side of the hæmatoma on the opposite side; in six cases there was severe contusion but it is significant that only three of these were temporal or frontal hæmatomas—the remaining three, as pointed out previously, were cerebellar. In other words, it is unusual for severe cerebral contusion to accompany a large supra-tentorial extradural hæmatoma.

There was no example of a bilateral extradural hæmatoma in the series nor of an accompanying large underlying subdural hæmatoma although such cases have been reported. A thin film of subdural or sub-arachnoid blood was present in five cases.

*Other Causes (2 cases).*—One patient had multiple fissure fractures of the skull which involved the anterior fossa and cribriform plate. He regained consciousness the day after his accident but three days later developed severe headache, neck rigidity and drowsiness. His condition rapidly deteriorated and he died the following morning. At autopsy there was a marked meningitis secondary to a dural tear over the cribriform plate fracture and a small right temporal extradural hæmatoma  $5 \times 3 \times 1.25$  cm.

The second patient died nine hours after injury. In addition to a large extradural hæmatoma which had been evacuated, there were multiple rib fractures on the right side with a hæmothorax and penetration of the lung. Death was due mainly to shock.



*Acute Subdural Hæmatoma*

Thirteen of the 21 patients with an acute subdural hæmatoma died, a mortality of 62 per cent. Table V shows that the cause of death in eight of the 13 was underlying cerebral contusion and laceration which is in contrast to the findings in the extradural cases.

*Cases Undiagnosed.*—Although there were four cases in the series where the subdural hæmatoma was not diagnosed before death, in only one was it likely that an operation would have saved the patient; of the other three, two had, in addition to large subdural collections, severe lacerations of the brain and multiple fractures in both anterior and middle fossæ; they were essentially fatal injuries and both patients remained in coma until death, one for five hours and the other for ten and a half hours after injury. In the third case death resulted from a sudden massive hæmorrhage into the mid-brain four hours after the accident which, although possibly related to pressure from the subdural hæmatoma, was more likely due to delayed rupture of an atheromatous cerebral vessel (q.v.).

*Intracerebral Hæmatoma (2 cases).*—The cases with gross cerebral contusion need not be described further. Two cases with intracerebral hæmatomas however, came to autopsy and although in the first case it was in the mid-brain and essentially fatal, in the second a subdural hæmatoma was adequately drained but the underlying large frontal intracerebral clot was not recognized.

34105/44.—This man, aged 77 years, was knocked down by a car. He was unconscious for 10 minutes, and at first examination showed no abnormal signs in the central nervous system. Four hours after the accident he suddenly had a decerebrate fit and became unconscious. The blood pressure rose to 200/110, and he had attacks of Cheyne-Stokes respiration. A lumbar puncture yielded a slightly bloodstained fluid under normal pressure. He remained in coma and died 36 hours after the accident.

At autopsy there was a linear fracture in the right middle fossa with some extradural clot, and a massive right subdural hæmatoma,  $10 \times 10 \times 3$  cm.; the origin of the bleeding was not clear. There was a little bruising of the brain beneath the fracture but the most striking feature was an extensive hæmorrhage into the mid-brain and pons, extending upwards to the sub-thalamic nuclei; the hæmorrhage had ruptured through into the IVth ventricle.

2086.—This man, aged 30 years, was involved in a lorry accident. He remained confused but improved until seven days after the accident, when he became more drowsy; a lumbar puncture showed that the C.S.F. protein had risen from 60 mgm. per cent. five days after the accident to 140 mgm. per cent. At operation on the eighth day a left subdural hæmatoma was found and washed out.

Following this operation the patient's mental state improved considerably and his right plantar response, previously extensor, became flexor. However, 13 hours after the operation he suddenly became comatose. The burr holes were opened again and a left temporal burr hole was made, but no further clot was seen. He died four hours later.

At autopsy there was some subdural blood over the left frontal pole, with contusion and laceration of the left frontal pole. The whole left hemisphere was œdematous and red with a marked pressure cone. On section of the brain a large intracerebral hæmatoma was present in the frontal lobe, which had flattened the anterior horn of the ventricle.

It is sometimes stated that the operative mortality of subdural hæmatoma in the first 24 hours after injury is so high that treatment over this period should be conservative. Since cerebral contusion plays such a large factor in these cases, it is obvious that the mortality is bound to be high; moreover, other severe injuries will be main or contributory factors and these patients, who are in the older age groups, withstand trauma poorly. Yet these should not be arguments against exploration in all cases where a subdural hæmatoma of sufficient size to cause compression is suspected. Although none of the six patients in this series operated on within the first 24 hours recovered, the autopsy findings show that the death of one patient was due to a ruptured liver; a second died from acute cerebral œdema which was very probably precipitated by intravenous fluid given for shock in a patient aged 66 years who had, in addition to his head injury, a fractured pelvis and a ruptured bladder; in another case the subdural clot was incompletely evacuated; a fourth patient, on admission four hours after the accident, was already in coma with fixed dilated pupils. Thus one cannot generalize from such figures, and the only safe rule is to explore, especially where there is evidence of deterioration of the conscious level following some improvement.

#### *Pulmonary Complications*

Patients in coma, from whatever cause, are very prone to develop a terminal inhalation or hypostatic pneumonia; for this reason frequent changes in the position of the patient and the prevention of inhalation of fluids and vomitus are important details in their nursing care. Some congestion and œdema of the lungs were the usual findings at autopsy, but seven patients had a definite bronchopneumonia (three with pulmonary fat emboli from injuries in other parts of the body) and one a pleural effusion. Nevertheless, although these were contributory causes, in only two patients were they considered the main cause of death. Both these patients were over 70 years; they died after evacuation of a subdural hæmatoma, one nine days later from acute pulmonary œdema, and the other 14 days later from bronchopneumonia.

However, the frequency of these lung changes is a measure of the care with which these patients must be nursed. There is no doubt that several deaths after acute head injuries, are due directly to the effects of inhaled vomit, blood and mucus at a time when the swallowing reflex is absent or seriously impaired. The fact that this complication was infrequent in this series was due to the nursing routine. Tube feeding was instituted in all cases where the swallowing reflex was diminished and, so long as the patient remained unconscious, the possible benefit of nursing the

patient with the head raised to lessen intracranial venous congestion was often sacrificed for the greater safety of keeping the patient lying on his side and flat, or even in some cases with the foot of the bed raised so that fluid or blood retained in the mouth would tend to trickle out rather than go down the trachea ; in this position also postural drainage of the lungs was effected, and this combined with suction was very beneficial.

### LATE RESULTS

Although recovery in the immediate post-operative period may be slow, yet a study of the late results shows that the ultimate prognosis is good. Thus of 12 patients with acute subdural hæmatoma and 26 with extradural hæmatoma which were followed up for periods of two to eight years, all returned to full work or to school.

Improvement continues steadily for the first two years during which time headache, lack of concentration and nervousness are common. Residual effects of dysphasia and hemiparesis may still be apparent to the patient although on routine examination recovery seems to have been complete. Thus a patient may still be conscious of a difference in the limbs or attacks of coldness over the affected side ; those who have been dysphasic may occasionally be lost for a word in conversation. After two years, although occasional headache was common, more than a third of the patients confessed to no headache at all and in only two did it remain a disability which forced them to have rests from work. In only two patients was there a residual hemiparesis remaining after several years.

Mental symptoms such as irritability, bad temper, and poor concentration improve steadily. Thus only four patients continued to have major symptoms ; three had attacks of severe depression, and one patient of 54 years who had had an acute subdural hæmatoma with cerebral contusion, developed a progressive dementia, though in this case there was a pre-traumatic psychiatric history.

*Epilepsy.*—No attempt has been made in this short review to subdivide the cases according to the type of hæmatoma or extent of the underlying brain damage. These factors are obviously of prime importance in determining the ætiology of the symptoms but it was found impossible to correlate them with any accuracy and it was considered wiser to give a general description of the late results of the group as a whole. An exception may be made, however, in discussing the incidence of epilepsy, since this is a matter on which advice is so often sought. Of the 12 patients with acute subdural hæmatoma, three had fits in hospital, either before or after operation, and in two, these have continued over two and three years, respectively, though they are very infrequent. Of 26 patients with extradural hæmatoma, four had fits while in hospital but have been free since, over periods of two to six years ; two others had their first fit about three months after the accident and continued to have them. It may be significant that in both these cases there was frontal lobe damage. In all, then, of 38 patients who recovered, only four have developed or

continued to have epilepsy once the immediate effects of the acute injury were over. It may be noted that the injury in these four cases was, respectively, a compound depressed frontal fracture with subdural hæmatoma, subdural hæmatoma with intracerebral temporal clot, a frontal extradural hæmatoma, and a compound depressed fronto-temporal fracture with extradural clot.

I think, therefore, that in the uncomplicated case of hæmatoma one may give a favourable prognosis both as to ultimate recovery and the likelihood of fits. As a group, however, there is an increased incidence of epilepsy and it is advisable to give a small regular dose of phenobarbitone for at least a year as a routine.

One should not be in too great a hurry to return the patients to work or to school. The children have done very well at school provided they were not sent back too soon; in the early days they were found to tire easily and to be irritable but with sympathetic understanding soon maintained their place with those of a similar age. Similarly for the adult, if light work can be arranged for a year after the injury one may fairly confidently give a good prognosis as to ultimate fitness for full work.

*Skull Defect.*—In a few cases of extradural hæmatoma, particularly where there has been a wide bony removal over the frontal or parietal regions, repair of the operative skull defect is required. Usually, however, the defect lies beneath the temporal muscle and repair is unnecessary. In children especially it is remarkable to observe, on seeing them some years later, that the defect feels hard and is unnoticeable.

### CONCLUSIONS

The main purpose of this lecture has been to examine the reasons for the high mortality of these hæmatomas and ways in which it might be reduced.

Delay before operation and the incidence of clots in sites other than the temporal region are major factors in the mortality of extradural hæmatoma. Some delay is of course inevitable, for not every accident occurs near hospital and, as we have seen, although the march of events in many cases is almost characteristic, in at least a third of them this is not so and the diagnosis is correspondingly difficult. Nevertheless, it should be realised that the difference between success and failure of operation may be measured in minutes rather than in hours. The high incidence of clots in atypical sites in this series renders the problem more complicated but the evidence suggests that a history of the nature of the accident, the position of scalp bruising and the site of fracture lines are reliable pointers to the hæmatoma, and exploration should be made with reference to these rather than by a routine practice of bi-temporal burr holes.

Acute subdural hæmatoma, by virtue of the underlying cerebral contusion, will always carry a high mortality. On this account others have advocated that the treatment, in the early stages at least, should be conservative. It must be admitted that the mortality in the first 24

hours is very high indeed ; but these are severe injuries, often with major injuries elsewhere in the body, so that many factors are involved and the only safe rule to adopt is to explore. I particularly wish to draw attention to that group of subdural hæmatomas where, after evacuation, pressure is unrelieved. An incidence of intracerebral hæmatoma of 11 per cent. in this series, their localised nature, and the successful results in those cases where they were evacuated, indicate that their recognition and radical treatment will reduce the mortality. The advisability of further operative measures in certain other cases has also been discussed.

The readier resource to burr hole exploration has undoubtedly led to the diagnosis of many cases which would otherwise have been missed : and indeed the differential diagnosis from other conditions which may simulate a surface hæmatoma, some indication of which has been given in the table of "negative explorations," can only be made in many instances by exploration. Nevertheless, we have seen that over these seven years under review, a hæmatoma was found in about 50 per cent. of the patients explored and within this time only three cases came to autopsy in which an undiagnosed hæmatoma was the main cause of death ; so that in practice the indications for exploration are usually clear-cut and a very useful diagnostic procedure need not be applied indiscriminately. Two points require emphasis : one, that an accurate description of the patient's conscious level at each examination is the most valuable single record that can be made after a head injury, for it is not only a reliable index of the patient's progress but often the first sign of a complication ; the other, that where to explore is as important as the decision to operate.

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# "OBSERVABLES" AT THE ROYAL COLLEGE OF SURGEONS

## 22. FRÈRE JACQUES

by

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"Frère Jacques, Frère Jacques,  
Dormez vous, dormez vous ?  
Sonnez les Matines, Sonnez les Matines,  
Ding, Ding, Dong, Ding, Ding, Dong."

AT THE END of the passage, beyond the President's room, and hung in so poor a light that the details are obscure, there is a portrait of Frère Jacques. Memory is so meagre that his achievements have passed beyond common knowledge but his memorial—a nursery rhyme—is secure. We, who are surgeons, should pause for a moment and look at that picture.

His story is set in France in the period which precedes and includes the reign of Louis XIV; the time was one in which great personalities dominated the scene but in which medicine stood at a low ebb. The doctors were acutely divided amongst themselves for the graduates of the two principal Universities were engaged in serious argument. On the one side were ranged the Parisians who followed the teachings of Hippocrates and Galen, and who were versed in the classical manuscripts of Greece and Italy, whilst upon the other stood the scholars of Montpellier who adhered to the beliefs of Arabia and the alchemy of the Spaniards. The science of both factions was entirely mediæval; each strove to dictate the ethics and the practice of medicine to the other and each was particularly concerned that its leading exponents should be appointed to the Royal household. The schism was so acute that the leaders of both sides forbade their followers to use the remedies advocated by their adversaries, and great was the joy of the Parisians when, in 1644, they succeeded in getting all the Montpellier graduates evicted from the capital by act of Parliament. This state of futile strife continued until the close of the seventeenth century, by which time wisdom was beginning to prevail and French medical practice became established upon strong scientific foundations. The gradual change was largely due to the wisdom of M. Fagon who was probably the most enlightened surgeon of his day and who in 1693 took up his appointment as surgeon to the King.

Throughout this strange period there are records of men who were not qualified as doctors but who, because of the circumstances and often because they were abetted by influential churchmen, such as Cardinal Richelieu, were able to treat the sick with as much chance of success as the professional surgeons. Such a one was Frère Jacques. Now it has often been held that he was a man of no consequence because he was judged by his contemporaries as ignorant and uneducated. This judgment has been accepted by later writers who described him as "an ignorant quack without any knowledge of anatomy." But it can be argued that, as his peers were shown by later scientific developments to be totally



Portrait of Frère Jacques (1651-1714) in possession of the College.

misinformed themselves, it was in fact to his credit that he took no stock of current beliefs. The criterion by which he should be judged is whether or not he treated the sick more efficiently than the surgeons of his day and whether he contributed to surgical knowledge.

His name was Jacques Beaulieu and he was born in the year 1651 in a hamlet called Etendonne. His parents were poor farmers and even as a boy he knew that he could never be satisfied with the squalor and ignorance of the peasants. At the age of 16 he had already made up his mind to seek out his own fortune in the world and to this end he had learned to read and write and had decided to be a surgeon. The chance to leave his home came when he fell ill and was transferred for treatment to a hospital at Lons-le-Saunier, and here, whilst he was convalescent, he did all he could to help the other patients and repeatedly asked to be taught how to bleed people.

His zeal did not meet with any response and, bitterly disappointed with what he had seen, he joined a regiment of cavalry and campaigned for several years as a trooper. It was during this time that he chanced to meet Pauloni, an Italian surgeon famous for operations for the stone, who took him as an apprentice. He travelled for six years in this capacity until he felt that he had learned all his master could teach and then he voyaged to Venice and to other Italian cities studying surgery ; but he was a poor

man and by the time he returned to Provence he had achieved little. Nevertheless, he pursued his ambition to practise surgery and for 10 years he treated the sick as a layman. By this time he was practising as a lithotomist and it was now that he began to experiment with the possibility of the lateral perineal operation which he went on to develop at Perpignon and Marseilles.

In the year 1690 he decided to change his mode of life ; he altered his name to Frère Jacques and became a monk ; but he did not join any of the recognised brotherhoods. His dress was distinctive and of his own design ; he wore a hat instead of a cowl and slippers upon his feet ; his vows were devised by himself and arranged to suit his occupation.

He returned to his home at about this time and after a short visit decided to move on again. Up till now his work had been done amongst the poor and he had acquired nothing to support him except his knowledge and experiences. It was about this time that he operated upon a canon at Besançon who advised him to go to Paris, which city was generally considered as the centre of all learning. The canon gave him letters of introduction to a colleague at Notre Dame and he arrived in the capital in 1697. The canon at the cathedral took Frère Jacques to M. de Harlai who was “senior president of parliament” and under whose chairmanship the surgeons of the Hôtel-Dieu were committed to examine and report upon all new candidates for medical licences.

Frère Jacques was destitute when he arrived in Paris, but M. de Harlai considered him to be honest and pious, and was impressed that he asked only a few sous for each operation “to repair his instruments and to mend his slippers.” He presented many testimonials from satisfied patients and he asked for permission to cut for the stone in Paris. He said that his desire was to advance knowledge, to cure the sick, and to teach others. The board regarded his proposition as insolent and him as an upstart, but, induced by curiosity and compelled by the chairman, they ordered that he be given a cadaver on which to demonstrate his practice.

This trial must have been more exacting than any demanded to-day for Frère Jacques was surrounded by adversaries, but he met the test without fear or confusion. He fixed the body upon a table and a stone was introduced into the bladder by opening the abdomen. He then passed a curved solid metal staff into the bladder and with this he displaced the latter towards the left side of the perineum. There was no groove upon this staff as there was upon the one Cheselden and others subsequently used. Then, taking a long bistoury, he incised the perineum two fingers internal to the tuber ischii and carried the incision forwards from the side of the anus. Subsequent dissections showed that it had passed between the “accelerator and erector muscles of the penis” without injuring either and that the side of the base of the bladder had been entered by cutting down on to the sound without opening the urethra. (It is my impression, having read several different accounts of this operation, that the actual details of how the prostate was negotiated are open



to question.) He then passed a finger into the bladder to locate and remove the stone ; if the latter was large he had devised a special instrument—a tenette—which he passed into the bladder along a dilator. In this way stones as large as hens' eggs could be extracted.

After the body had been dissected the board declared that the incision was sound but they were unanimous in their decision that he should not be granted a licence ; their opinion was based upon the fact that he ignored the accepted ritual of surgical operations. There can be no doubt that lateral lithotomy, even in its crude form, was a safer procedure than the method in common use which was called the " apparatus major." In this operation the urethra was opened below the prostate, the external sphincter was divided, the prostate was split digitally or with a dilator, which violently contused the tissues, and the stone was dragged out through a small hole in the middle of the perineum.

Disillusioned and sad, Frère Jacques left Paris in 1697 and went to Fontainebleau where the Court was in residence. Here he met and impressed M. Duchesne who was a leader of medical thought and who spoke favourably to M. Fagon (consulting surgeon to the King), to M. Bourdelot (medical adviser to the Duchess of Bourgogne), and to several other influential people who agreed that they must see him operate upon a patient.

Now it happened that a few days later a shoemaker's apprentice, having a stone in the bladder, consulted M. Duchesne who straightway placed the lad in custody in preparation for the trial. Frère Jacques operated upon this boy in the presence of M. Duchesne and of M. Felix (another surgeon to the Royal Household) and convalescence was so uneventful that the patient was cured within three weeks. This operation brought great applause ; the King was notified of its result and he immediately gave instructions that Frère Jacques was to be lodged with Bontemps—his valet—and he was given the King's licence.

Then began a short period of prosperity in which the common citizens of Paris acclaimed him as a great physician sent by God to heal their scourge. Six successful operations were performed and in one of these he removed a stone from the bladder of an Irishman who had been wounded in the lower abdomen 18 years previously. The calculus was a rifle ball encrusted with crystals.

Frère Jacques showed great simplicity of bearing and all who came to see him were impressed by his calm courage. This was especially noticeable because his fame was such that whenever he operated he was surrounded by such a tumult of spectators that a guard of soldiers was provided to maintain order. But his success was short lived. On the 10th April, 1698, he operated upon a boy aged 16 in the Hôtel-Dieu and the patient died. Frère Jacques worked at this hospital by Royal Command and his position in relation to his professional colleagues was not happy ; so it was that M. Méry, the senior surgeon, sent a report to the Archbishop of Paris and affirmed that of the eight patients upon whom

they had watched him operate two had died shortly afterwards, one had had the rectum opened and one had suffered the same injury to the vagina. From then onwards he was only allowed to work under supervision ; but in spite of this he performed lithotomies on 42 patients at the Hôtel-Dieu and 18 at the Charité Hospital. Twenty-five of these people died and he was forbidden to practise any more.

The operation which Frère Jacques had practised up till now was not accurate and there were legitimate grounds for criticism. He had had numerous failures and M. Merius and M. Dionis presented another report in which they affirmed that upon occasion he had cut away the urethra from the base of the bladder, divided the muscles of the perineum, transgressed the vagina and the rectum, damaged large arteries and caused much suffering by faulty diagnosis and bad operative technique. Against this indictment it must in fairness be recorded that even in its form at that time his operation was probably better than the “*apparatus major*,” that his diagnosis was not worse than that of his critics, and that his after-treatment—or the lack of it—was preferable to that of the recognised surgeons. An English surgeon, Mr. Proley, who saw him operate on 2nd August, 1698, wrote “that the surgeons of Paris greatly ran down Frère Jacques notwithstanding that they did copy his methods.”

Referring to this time Bayle and Thillaye tell how everybody began to despise him and to say that his calmness was born of ignorance. His temerity was said to be so great that he was a man who felt that he could disregard all previous learning. He paid no heed to pre-operative bleeding or to purging—which were considered proper at the time—he used no astringents or detergents and preferred only to prescribe a little oil or wine, saying, when questioned about his disregard of ancillary treatments, that, when he had removed the stone, God would heal the wound. In spite of all this criticism one of his biographers writes—“one cannot help remarking that if he had been encouraged as he was censured his methods must have prevailed.”

For the second time he left Paris and in 1698 came to Orleans, whence he travelled to Aix-la-Chapelle and so on to Amsterdam in all of which cities he did a number of lithotomies. In Amsterdam, after a short period, during which he performed many successful operations, he was introduced by M. de Bonrepos—the French Ambassador—to his Most Christian Majesty, who straightway proclaimed him as the leading lithotomist in the land. Meanwhile, back in France, M. Fagon, who himself suffered from stone, began to study Frère Jacques’ methods personally. And the more he thought about it the more convinced he became that lateral perineal lithotomy was a proper operation. Eventually Frère Jacques was persuaded by him to come back to Versailles and together with M. Fagon he operated experimentally upon many bodies. As a result of these anatomical trials M. Fagon satisfied himself as to the soundness of the anatomical approach to the bladder but he felt that the safety of the operation would be enhanced by using a grooved staff

upon which to cut. In 1701 M. Fagon admitted a number of patients to the Charité de Versailles upon whom he and Frère Jacques operated with such success that many other surgeons were converted to their views. The details of the operation—using the grooved staff—were published by Frère Jacques in a brochure at that time. The test of M. Fagon's faith in lateral perineal lithotomy came when he himself had to undergo the operation and it is recorded that he requested Frère Jacques to remove his stone, but that his family forbade it and M. Mareschal eventually performed the operation successfully.

In 1702 he performed successful lithotomies upon M. Pignerol, a famous *maître d'academie*, and upon M. le baron de Saint Denis and was accordingly awarded a certificate of efficiency by the Master Surgeons of the Royal Charity Hospital of Versailles. He also treated 38 other patients all of whom are said to have been cured.

In 1703 he reached another dangerous corner for the Maréchal de Lorges—who suffered from stone—asked him to remove the offence. The Marshal was a cautious man and before submitting to his own ordeal he watched Frère Jacques treat 22 poor patients. These survived but the Marshal died and disgrace again confronted him. He went in despair to Geneva where, after a little time, he performed a number of successful lithotomies and was honoured by the Republic.

In 1704, being pressed by important people, he returned to Amsterdam where he practised with success. Later he left Amsterdam for Brussels, where he continued to practise lithotomy and was so much esteemed that he was presented with the gold medal, which he is wearing in his portrait, and by public subscription the common citizens raised a gift to the value of £400.

For the next 10 years he practised lithotomy in Geneva, Nancy, Liège, Strasbourg, Vienna, Venice, Padua and Rome—where he was received and honoured by the Pope—until at the age of 69 he returned to his own village; on the 7th December, 1714, he died in the house of his friend Laurent Decart. In his will he left much money, a great deal of which he directed to various charities.

This is the history of a most singular man to whom surgery owes a great deal. He is said to have operated upon 4,500 patients for the stone and another 2,000 for hernia in the short span of 19 years which cover his period as an active surgeon. His work was certainly modified by his association with M. Fagon and I do not doubt that after he had gone to Versailles his operation was much improved in technique and result.

After Frère Jacques, Cheselden (1688-1752) and other famous surgeons trod the same ground in England and in Europe and the light he lit guided them to perfection. But more than this he showed courage and a dignified bearing in the face of powerful critics; in contrast to the custom of his time he relied upon nature to heal the wounds he had made. He was calm and quiet when he operated, and he treated the poor and the humble to the utmost of his skill. His mistakes were not so much his

own as those of the period in which he lived and his contributions to knowledge were ahead of current beliefs. He gave to those who followed him an operation and an example of behaviour.

### GIFT FOR RESIDENTIAL COLLEGE

The Royal Australasian College of Surgeons has donated £340 in Australian currency (£276 3s. 9d. sterling) for a piece of furniture for the new residential quarters in Lincoln's Inn Fields.

The President and Council much appreciate this very kind gift.

### MONTHLY DINNERS

Monthly dinners are held in the College on the Wednesday before the second Thursday of each month. The following are entitled to attend with their guests: All Diplomates and students of the College and Members of the Associations linked to the College through the Joint Secretariat. It is not necessarily intended that guests should be members of the medical profession.

The dinners will be at 7 p.m. on the following Wednesdays: November 9, and December 7, 1949, January 11, February 8, March 8, April 12, May 10, and June 7, 1950. There is an inclusive charge of £1 5s. (including drinks), which must be sent with the application to the Assistant Secretary at least a week before the date of the dinner. The dress is Lounge Suit or Uniform.

### DIARY FOR OCTOBER (17th-31st)

Mon. 17	10.00	MR. A. D. MARSTON—History of Anæsthesia.
	11.15	MR. A. D. MARSTON—History of Anæsthesia.
	5.00	DR. B. L. S. MURTAGH—Avoidable Accidents.
Tues. 18	10.15	DR. H. G. EPSTEIN—Physics in Anæsthesia.
	11.30	DR. H. G. EPSTEIN—Physics in Anæsthesia.
	5.00	DR. GEORGE EDWARDS—Pre-operative Medication.
Wed. 19	10.00	DR. E. S. ROWBOTHAM—Continuous Spinal Analgesia.
	11.15	PROF. E. A. PASK—Respiration.
	5.00	PROF. E. A. PASK—Respiration.
Thur. 20		Lectures on Basic Sciences begin.
	10.00	PROF. E. A. PASK—Circulation.
	11.15	PROF. E. A. PASK—Circulation.
	5.00	DR. JOHN HEWER—Anæsthesia for Neurosurgery.
	5.00	PROF. V. DIX—The Conservative Treatment of Hydro-nephrosis.
Fri. 21	10.00	DR. H. L. MARRIOTT—Fluid Balance.
	11.15	DR. H. L. MARRIOTT—Fluid Balance.
	5.00	DR. W. W. MUSHIN—Local Analgesia.
Mon. 24	10.00	DR. W. W. MUSHIN—Local Analgesia.
	11.15	DR. W. W. MUSHIN—Cyclopropane and Absorption Technique.
	5.00	DR. W. W. MUSHIN—Cyclopropane and Absorption Technique.
Tues. 25	10.00	DR. C. A. KEELE—Pharmacology.
	11.15	DR. C. A. KEELE—Pharmacology.
	5.00	DR. A. H. GALLEY—Caudal Analgesia.
	5.00	MR. E. S. R. HUGHES—Arris and Gale Lecture—Development of the Mammary Gland.*

# DIARY

Wed. 26	10.00	DR. C. J. MASSEY DAWKINS—Epidural and Posterior Splanchnic Block.
	11.15	DR. T. CECIL GRAY—Relaxant Drugs.
	5.00	DR. T. CECIL GRAY—Relaxant Drugs.
Thur. 27	10.00	DR. FRANCIS T. EVANS—Anæsthesia for Perineal Surgery.
	11.15	DR. I. W. MAGILL—Intubation.
	5.00	DR. E. H. RINK—Anæsthesia for Cardiac Surgery.
	5.00	MR. A. E. W. MCLACHLAN—Bone Syphilis.
Fri. 28	10.00	DR. W. S. MCCONNELL—Nitrous Oxide and Vinesthene for Dental Surgery.
	11.15	DR. A. I. PARRY BROWN—Anæsthesia for Thoracic Surgery.
	5.00	DR. A. I. PARRY BROWN—Anæsthesia for Thoracic Surgery.
Mon. 31	10.00	PROF. SPURRELL—Anoxia.
	11.15	PROF. MACINTOSH—Volatile Anæsthetics.
	5.00	PROF. MACINTOSH—Volatile Anæsthetics.

## DIARY FOR NOVEMBER

Tues. 1	10.00	PROF. R. R. MACINTOSH—Volatile Anæsthetics.
	11.15	DR. RONALD WOOLMER—Convulsions.
	5.00	DR. RONALD WOOLMER—Therapeutic and Diagnostic Applications of Anæsthesia.
Wed. 2		Final F.D.S. Examination begins.
	10.00	DR. R. W. COPE—Anæsthesia for Children.
	11.15	DR. VERNON F. HALL—Anæsthesia and Analgesia in Obstetrics.
	5.00	DR. VERNON F. HALL—Anæsthesia and Analgesia in Obstetrics.
Thur. 3	10.00	DR. P. J. HELLIWELL—Refrigeration and Electro-narcosis.
	11.15	PROF. JOHN KIRK—Anatomy of the Neck in relation to Anæsthesia.
	5.00	PROF. JOHN KIRK—Anatomy of the Abdominal Wall in relation to Anæsthesia.
Fri. 4	10.00	DR. W. D. WYLIE—Pulmonary Complications.
	11.15	DR. JOHN GILLIES—Total Spinal Block.
Mon. 7		Final Fellowship Oral Examination (General Surgery) begins.
Wed. 9	5.00	Annual Meeting of Fellows and Members.
Thur. 10	5.00	MR. V. ZACHARY COPE—Bradshaw Lecture—Visceral actinomycosis and its treatment.*
Fri. 11		D.A. Examination (Part I) begins.
Wed. 16		D.T.M. & H. Examination begins.
Thur. 17	3.45	MR. R. J. LAST—Arnott Demonstration.*
Fri. 18		D.A. Examination (Part II) begins.
		Board of Faculty of Dental Surgery.
Tues. 22	3.45	DR. JAMES CRAIGIE—Imperial Cancer Research Fund Lecture*
Fri. 25	5.00	SIR HENRY WADE—Thomas Vicary Lecture.
Tues. 29	3.45	DR. C. H. ANDREWES—Imperial Cancer Fund Research Lecture.*
Wed. 30		Second L.D.S. Examination begins.

\* Not part of courses.

A series of Tutorials in Anæsthetics will also be held during the same period as the Lectures (October 17—November 4), and will consist of 10 one-hourly periods, commencing at 6.15 p.m.

# TREATMENT OF BURNS

Lecture delivered at the Royal College of Surgeons of England  
on  
5th October, 1948  
by

A. B. Wallace, F.R.C.S.E.

Lecturer in Plastic Surgery, University of Edinburgh

## PATHOLOGICAL PHYSIOLOGY

THE TREATMENT OF BURNS is essentially therapy applied to the pathological physiology and, therefore, the salient features of the disturbed physiology following a burn will be described. ✓

Throughout the burned area the capillaries and venules are dilated and from them fluid escapes on the surface and also accumulates in the extravascular spaces, a condition which may last for 48 hours. This exudation of fluid into and from the surface of burned tissues is significant for two reasons. First, it is an important cause of shock, and secondly, its persistence delays healing and return to function. Work by Glenn *et al.* (1942) has shown that sustained swelling in burned parts depends largely upon the deposition of coagulated exudate, which collects and holds a maximum amount of water delivered to the tissues from the injured blood capillaries: the less the formation of coagulum, the less sustained the swelling and the quicker the healing.

If the dermis is not completely destroyed, sufficient epithelial elements remain in sebaceous and sweat glands and in hair follicles to form a complete covering within three weeks. In deep burns a layer of granulations forms between living and dead tissue and gradual separation of the slough takes place to leave a granulating surface.

When a large area of skin surface is involved, considerable systemic disturbances arise. In a few patients an immediate state of primary or initial shock is demonstrable: it resembles the vaso-vagal syndrome. In the first 12 to 24 hours there is often failure of the peripheral circulation—the condition of shock (oligaemic shock)—as a result of the vascular changes in the burned areas. The leakage of plasma through the capillaries results in a diminution of plasma volume and consequent hæmoconcentration. To ensure adequate circulation to the heart and central nervous system, the reduced whole blood volume is redistributed by vasoconstriction in other organs. In deep burns there is a destruction of red blood cells.

With the return of the capillary walls to normal, the œdema tends to subside, and hæmoconcentration, blood pressure and blood volume to return to normal.

Metabolic disturbances are indicated by a rising non-protein nitrogen content in the plasma—especially of the amino-nitrogen, by hypoproteinæmia and by increased urinary excretion of nitrogen. Loss of nitrogen in the exudate from the burned surface may also be considerable.

In spite of adequate intake, the kidneys may not meet the demands made upon them. The cause of the renal failure may be manifest—e.g., badly controlled sulphonamide therapy, hæmolysis of red cells as a result of the thermal injury or following an incompatible transfusion. Anuria may occur in the absence of such causal factors and an explanation may be found in an impairment of function of the renal parenchyma from ischæmia. The ischæmia may result from the reduced renal blood flow which occurs in oligæmic shock. A state of hypotension in oligæmic shock persisting beyond 40 minutes might of itself lead to renal damage with depression of urinary output persisting when the general blood pressure is restored. Another factor which might produce the ischæmia is spasm of the renal arterioles.

In a considerable proportion of extensive and moderately extensive burns in children, there is a hypertensive phase which may be associated with oliguria and even anuria. Renal damage, though suspected, has seldom been demonstrated in fatal cases. The hypertensive response must be regarded as an exaggeration of the normal compensatory response to loss of blood volume.

### BACTERIOLOGY

Because of the relatively large raw area of damaged cells, extensive burns are readily infected. Infection may arise from many sources. The extent of infection depends on the resistance of the patient, the virulence of the organisms, the amount of necrotic tissue, and the degree of immobilization, and the dryness of the surface.

The bacterial flora is characteristic. Before treatment the *Staphylococcus albus* is often present. After first-aid treatment a variety of organisms may be observed: *Staphylococcus aureus*, Coliforms, *B. subtilis* group, the enterococcus and, sometimes, the hæmolytic streptococcus. In hospital the organisms to be guarded against are hæmolytic streptococci and *Staphylococcus aureus*; usually they appear during the first week. In the second to fourth week when sloughs separate in deep burns, mixed coccal and bacillary infections are frequent; the most common are coliforms, *B. proteus* and *Ps. pyocyaneus*. In the later granulating period the infections are mainly coccal.

### PRE-OPERATIVE MANAGEMENT

The chief objectives are to save life, to immobilize the part, to allow the body every chance to resist infection and to set up a very strict nursing routine for the patient. The practical steps can with advantage be put on a chronological basis as follows:—

- (1) To relieve pain, to relieve thirst, to prevent loss of heat.
- (2) To do no further injury to skin tissues which, though damaged, may still be viable.
- (3) To limit bacterial invasion of the burn by immobilization.
- (4) To limit œdema by posture: in extensive burns by pressure.

- (5) To counter "burn shock" by adequate "replacement therapy" with blood and plasma or serum, and to attend thereafter to the correction of the metabolic disturbances which follow burning, by prescribing appropriate intake.

On admission the patient is covered with a sterile cloth, put to bed and wrapped in blankets. Heating must be carefully controlled; if too vigorous it will inhibit the compensatory vasoconstriction. Drinks of sweet tea, orange juice, and glucose saline are provided. The pulse, the temperature, respirations and blood pressure are recorded and blood concentration estimated. If morphine has not been administered previously, a suitable injection of the sulphate is given. A warning must be offered to avoid large doses; an adult should receive an injection of gr. 1/6; a child of six years an injection of gr. 1/24.

Following the administration of the sedative, the patient is left undisturbed for 30 minutes. Thereafter an estimate of the extent of the burn is made. The blood pressure and blood concentration are once again determined, pulse and respiration rate and temperature recorded and the degree of shock is assessed. The onset of oligæmic shock must be anticipated and, if possible, prevented. If it is already established or if the burn is extensive, a transfusion of blood or human plasma or serum is set up immediately to restore the normal volume of circulating blood. If whole blood is administered within the first 48 hours the anæmia which often develops during the first week of a burn is prevented. In spite of plasma administration, it is not unusual in deep and extensive burns on the fourth or fifth day to find a low plasma protein level. Evans and Bigger (1945) have shown that if large amounts of blood are given from the beginning, the optimum level of plasma protein may be maintained. They suggest that eight grammes of sodium bicarbonate should be given orally for every pint of blood. One pint of blood is administered for every two of plasma.

A warning, however, must be given. Following blood transfusion, two young patients of the writer died about 48 hours after scalding. The blood was from universal donor group O and was apparently compatible. Sections of the kidneys revealed typical "transfusion reactions." It is possible, as suggested by Ham *et al.* (1948) that with the increased fragility of red blood cells following burns, the administration of plasma containing incompatible agglutinins might lead to an increase in the osmotic fragility of the red cells—e.g., in patients with blood group A or B, who receive whole blood of group O. It is probably advisable to administer blood of the homologous ABO group and not administer the universal donor group O blood as a routine.

A daily intake and output chart must always be kept. All urine must be saved and examined chemically and microscopically. An output of at least three to four pints is aimed at in 24 hours.

Various methods of calculating the desired dosage of intravenous fluid have been suggested but personal experience is the safest guide. In an



adult the administration of intravenous fluid must be considered in every burn with 15 per cent. or over of the body surface involved : in children, the need is more urgent and a child with a burn of 10 per cent. of the body surface may require intravenous resuscitation. A young patient demonstrating a hypertensive response is in more urgent need of fluid than one with a low blood pressure, since the pressure is apt to fall suddenly and without warning, and is peculiarly resistant to all methods of restoration.

In adults the blood pressure value is the best indication of the general condition of the patient. As a rough guide, when the blood pressure readings are normal, one pint (568 c.c.) of plasma is given within a space of 20 minutes, followed by a second pint of plasma and a third pint of blood at a slower rate. When the blood pressure reading is low, at least two pints of plasma are transfused rapidly (within a period of 20 minutes) and then blood and further plasma administered at a slower rate. When the blood and pulse pressures are stabilized, local treatment may be begun, but intravenous infusion of plasma should be continued for at least 24 hours.

In children, the general condition must be assessed from all angles. At frequent intervals estimates are made of temperature, pulse and respiration rate, blood pressure and the degree of hæmoconcentration. After extensive investigations, Morrison (1947) proved the hæmatocrit to be the most valuable single criterion of plasma loss. The amount of plasma loss was calculated as in the following example :—

*C. R., aged two years*

Normal hæmatocrit for age	..	..	..	..	..	35 per cent.
Normal blood volume for age	..	..	..	..	..	750 c.c.
Normal plasma volume for age	..	..	..	..	..	480 c.c.
Abnormal hæmatocrit (2½ hours after scalding)	..	..	..	..	..	50 per cent.

Let abnormal blood volume = X c.c.

Then (if total red-cell volume R is constant) :—

$$\frac{35 \times 750}{100} = R = \frac{50 \times X}{100}, \quad \text{Therefore } X = \frac{35 \times 750}{50} = 525 \text{ c.c.}$$

Therefore amount of plasma lost over 2½ hours = 750—525 c.c. = 225 c.c.

The rate of transfusion can, therefore, be regulated hourly to restore the circulating blood volume.

If large transfusions are required to restore the blood pressure, the neck veins are scrutinized for over-prominence and the lung bases periodically examined.

The second objective is to allow the body every chance to resist infection which may occur locally or in the respiratory tract.

*Penicillin administration.* The early administration of penicillin systemically is the most valuable protection available. In addition to limiting infection, it would appear to encourage the early separation of

sloughs. This probably is brought about by the upward rapid growth of deep gland elements which leads to earlier separation than would the digestive process of the leucocyte enzymes. Penicillin should be given intramuscularly in all deep burns, in all burns of the face and hands and in burns of the air passages, either by a continuous drip method or intermittently every three hours.

*Rest.* In addition to penicillin there are other weapons to combat infection. Probably the most important is *rest*, *rest* of the injured part. "Rest, so apparently simple," as John Hilton wrote, "as to make one almost apologise for selecting it." He continued, "rest is the necessary antecedent to the healthy accomplishment of both repair and growth."

*Resistance of patient.* Closely associated with the benefit from rest is the value of the natural resistance of the patient. This factor has been lost sight of. Fear of the bacterial world is widespread. Protection is sought through antiseptics, and from the many processes of sterilization. For many years the human body has had little chance to demonstrate its own power without some interference. Local applications have disturbed the natural healing processes; antiseptics applied to raw surfaces have caused further injury to already damaged tissues; local medicaments have tended to keep the raw surface moist or even sodden, a state suitable for the multiplication of micro-organisms; improper immobilization and active movement have encouraged the invasion of surface-infecting organisms; and contamination of the burn has resulted from thoughtless positioning which has rendered impossible the application of strict nursing principles.

### LOCAL CARE

To assist the natural defences of the body, a burn should be cleansed with bland solutions only, and thereafter kept dry; the affected part should be immobilized and be positioned to allow of strict nursing care.

Before describing the details of local treatment two further practical points must be considered, the maintenance or restoration of function and the restoration of a normal appearance. The latter will not be deliberated in any detail but steps can be taken from the first to achieve the former.

Delayed healing and return of function in burned parts may result from persistent œdema fluid in which a coagulated exudate has formed. This phenomenon is commonly manifest in burned extremities.

The principles in local treatment can be summarized: ✓

- (1) To cause no further local trauma with irritating local applications.
- (2) To encourage the natural barriers to infection: ✓
  - (a) by keeping the burned area dry.
  - (b) by immobilization of the affected part.
- (3) To control local œdema around the burn and the escape of fluid from the burned surface by:
  - (a) pressure dressings, and/or
  - (b) elevation of the part.

- (4) To encourage return of function by allowing free movement as soon as possible after ten days.
- (5) To assist the separation of sloughs.
- (6) To skin graft in deep burns as soon as possible. ✓
- (7) To treat the protein deficiency, anæmia, and cachexia which may follow severe burns, especially those heavily infected in the sloughing state.
- (8) To ensure satisfactory rehabilitation of the patient and provide any necessary follow-up treatment, including X-ray therapy for keloid and plastic surgery to restore function and appearance.

Local treatment is embarked upon when the blood pressure is stabilized. A preliminary injection of atropine sulphate is given. Light general anæsthesia is recommended, preferably by cyclopropane, but if this is not available, by gas and oxygen, supplemented if necessary with ether. The services of an experienced anæsthetist are essential especially in burned children. Inhalation anæsthesia is sometimes avoided and scopolamine and morphine are given by injection.

Before cleansing, swabs for culture are taken from the burn and the surrounding skin. The cleansing or "plenary" treatment is carried out in a warm operating theatre. Precautions are taken as for a major surgical operation. Cap, mask, gown and gloves are worn by the surgeon, and the burn, if necessary, is treated in sections to avoid prolonged exposure. Speed is combined with gentle thoroughness. The surrounding skin and the burn are cleansed with 1 per cent. cetavlon. Cetavlon is a synthetic detergent, cetyl-trimethyl ammonium bromide, which apparently reaches the organisms in the depths of the sweat and sebaceous glands and hair follicles; it has a rapidly lethal action on hæmolytic streptococci; it is relatively non-toxic but (1) its action is impaired in the presence of blood, and (2) it causes (even in solutions of 0.1 per cent.) lysis of leucocytes (Barnes, 1946). The cetavlon is applied by swabs which are swept from the centre of the burn towards the edges to wipe off the raised epidermis. The cetavlon is washed off with saline and the burn dried with gauze. If cetavlon is not available, the plenary treatment is carried out with gauze wrung out of warmed white soap solution or warm normal saline.

The cleansing process described above, or some modification, is adopted by most surgeons but opinions vary as to the further local care. Each case must be considered individually and no one method of local treatment can be adopted with success in every form of burn encountered.

*Pressure dressings.* For some years the writer has employed this method of treatment and found it one of the most generally applicable and successful; the advantages are (1) the patient is comfortable; (2) in superficial burns healing has taken place by the time of the first dressing; (3) œdema is limited; and (4) return to function is early.

Pressure dressings have given satisfaction in most anatomic regions, especially in the hands. The fingers have vaseline bandages applied to each separately and the position of function is moulded around a suitably shaped mass of wool on the palmar aspect of the hand. Position and pressure are maintained by the addition of further wool and the application of a crêpe bandage (Fig. 3). A plaster bandage is then applied to produce immobilization and assist elevation. The term "pressure bandage" is apt to imply that the benefits from the method arise from the pressure of the bandage over the wool. In the opinion of the writer more important factors are : (1) the encouragement of a dry burn surface by the absorptive dressings and wool, and (2) the immobilization which accompanies the method. Speaking generally, any method of treating burns which produces these two conditions will lead to encouraging results.

In general, pressure dressings, combined with systemic penicillin administration and local immobilization and careful positioning for nursing care, have given every satisfaction except in burns of the face and neck. The dressings of burns of the face and neck, especially in babies and young children, are difficult to keep dry and frequently are the cause of worry and disappointment. About 12 months ago, a departure from pressure dressings was made for burns of this region and the "exposure method" encouraged. The results were in some ways dramatic. The method has been applied to most other regions and has proved almost equally efficient. No originality is claimed since exposure treatment was described many years ago though of recent years it has been modified to the very controversial "dry heat" method.

The following is a preliminary report of an attempt to simplify the present somewhat complex outlook on the control of burns. It is not intended to add yet another modern method to the treatment pool.

### *Exposure Method*

The principles are :

- (1) To keep the raw area dry and so prevent the multiplication of surface-contaminating organisms.
- (2) To immobilize the part to prevent invasion of the tissues by infecting micro-organisms.
- (3) To administer penicillin systemically to counter any tendency to general and local infection.
- (4) To render nursing care as simple as possible.

The patients are nursed in a general surgical ward. Ventilation is adequate but draughts are avoided. The ward temperature is registered twice daily.

Following cleansing, the burn is dusted with powdered penicillin. The dusting is repeated every four hours for the first 24 hours, thereafter when necessary. In view of possible absorption the powder should not be diluted with any of the toxic sulphonamide drugs. Early in the series one young patient developed a cyanosis which could be attributed only to

absorption of sulphonamide. The burns are not covered in any way but left exposed to the air. The ward is swept four times in the 24 hours. The surgical and nursing staff wear masks only when dressings are carried out. All manner of organisms must fall on the surface of the burn, yet infection does not supervene. The crust for the first 24 hours is light brown, thereafter becoming progressively darker. A characteristic feature is the rarity of any reactionary blush of the surrounding skin.

Penicillin is administered intramuscularly every four hours in doses of 500,000 units per diem.

The treatment is in some ways simple to carry out but care and ingenuity are required to obtain satisfactory immobilization and to permit free exposure of the affected part. Though the routine appears simple, the nursing care is no less exacting. To ensure success, nursing and surgical staff must act as a team so that all details in treatment are effected and control is rigorous. Splinting of certain parts is simple to accomplish and complete immobilization can be assured. In parts such as the face and neck, immobilization is relative. Nursing care in the first 48 hours concentrates on the elimination of disturbing elements which would delay the natural tender crust from becoming more tough and resistant and less prone to tear from shearing strains. This can be attained only by team work.

The first regions to be treated by exposure were the head and neck. Neck burns were positioned in slight hyperextension. The outstanding



A



B

Fig. 4. (a) Extensive facial burns treated by exposure. (b) Twelve days later.

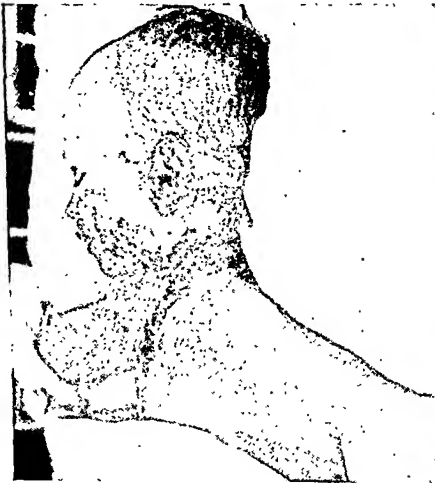


A



B

Fig. 5. (a) Extensive facial scalds treated by exposure. (b) Eighteen days later.



A



B

Fig. 6. (a) Scalds of face, neck and chest treated by exposure. (b) Twenty-one days later.

feature was the early separation of the scab. Then the method of treatment was extended to burns of other parts of the body (Figs. 4, 5, 6).

When the buttocks or lower extremities are involved, some form of suspension is applied—e.g., skin or pin traction. This positioning renders nursing care simple (Fig. 7). One case deserves description in some detail :

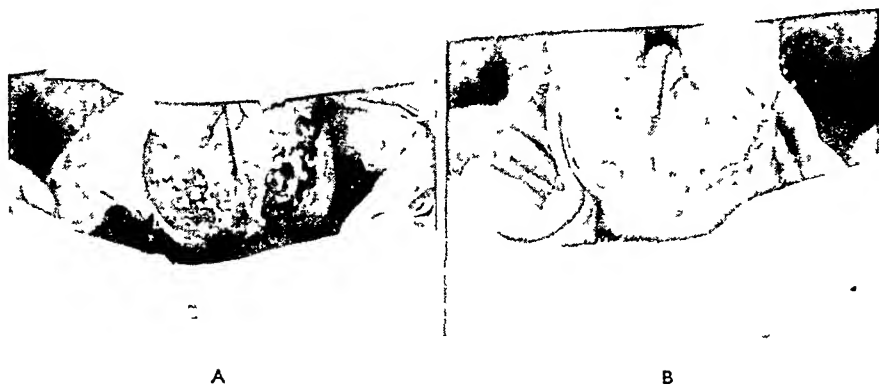


Fig. 7. (a) Scalds of buttocks treated by suspension and exposure. (b) Twenty-one days later.

*W.H.*, was aged three weeks on admission. This baby had both lower extremities partially cooked from fire. Pressure dressings were applied but were difficult to keep dry and free of contamination. For the first few days the child's general condition was poor in spite of transfusion. On the third day the burn was re-dressed. There was obvious loss of skin beyond the upper third of the thighs and there was gangrene of the toes. To permit the exposure treatment of the burns, pins were inserted through the calcanei (Fig. 8 (a)). From that day the baby improved. Dry crusts formed over the affected areas. On the 26th day the crusts were removed surgically and postage stamp grafts applied and fixed with pressure dressings. The child's condition once again gave cause for anxiety and four days later the dressings were removed. All the grafts on the left leg had taken but about 30 per cent. only on the right leg. Tulle gras and saline dressings were applied. The child made little headway and the dressings showed evidence of a persistent blue tinted discharge. The limbs were again exposed and left in suspension only. Once again the child made a dramatic improvement, maintained till the 37th day when sloughing of the soft tissues exposed the right knee joint. An above knee amputation was carried out. The baby is now well and thriving rapidly (Fig. 8 (b)).

The lesson from this case is undoubtedly the value of exposure which leads in turn to a dry surface, prevention of multiplication of organisms and diminished absorption. Whenever toxic absorption was permitted the baby's condition deteriorated.

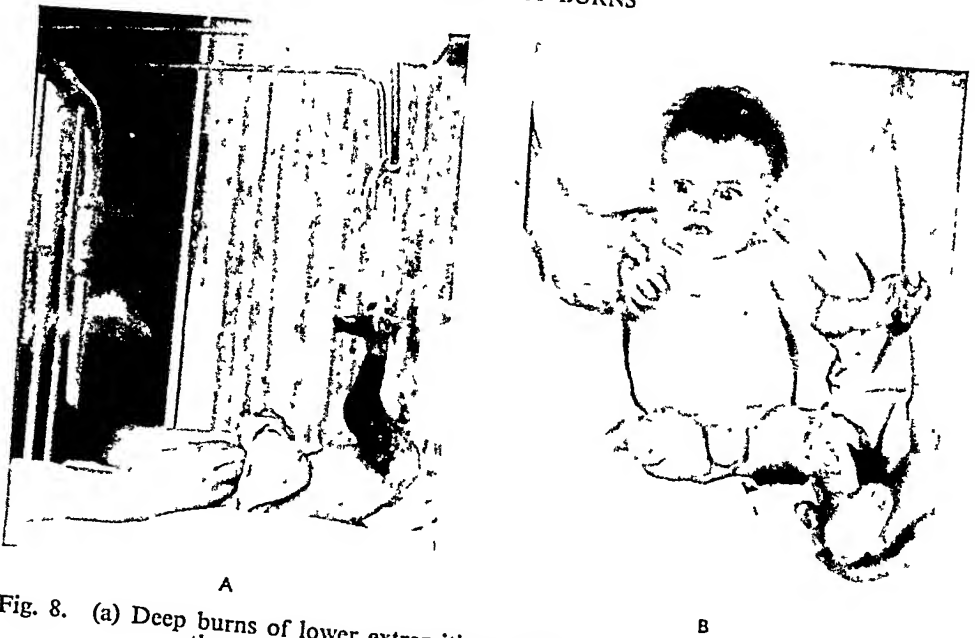


Fig. 8. (a) Deep burns of lower extremities treated by suspension with pin through the calcanei and exposure. (b) Two months later.

Positioning of burns of the upper extremity to obtain exposure, immobilization and suspension, is difficult. The form of fixation is dependent on the site of the burn. Where possible, skin traction, or a narrow plaster slab, is applied along a strip of uninvolved skin and the limb suspended (Fig. 9).

When the hand is burned, a nail or pulp traction stitch can be inserted through each finger and led to a square wooden "spreader" with regularly placed perforations. The stitch ends are drawn through the perforations on the "spreader" and tied so as to suspend the hand as nearly as possible in the position of function (Figs. 10, 11). If the fingers are not involved, suspension is accomplished through stockinette fingers dipped in collodion.

Patients with burns of the chest, abdomen and genitalia are nursed on the unaffected aspect of the body (Fig. 12). Where beneficial, children are placed on a Bradford frame suspended in a manner similar to that used in the pressure dressing method.

### DISCUSSION

The benefit of pressure dressings in the early care of burns has been proved by many surgeons and elaboration at this point is not indicated. The burns treated in this series by the exposure method have, in the main, been superficial, but close on 300 patients have been dealt with.

The most extensive burn so far treated was one involving the left upper extremity, left chest and abdomen, and left lower extremity (Fig. 13).





A



B

Fig. 9. (a) Scalds of upper arm and chest treated by suspension and exposure.  
(b) Twenty-one days later

Shock was controlled with the necessary intravenous fluid and the burns treated by exposure in the usual manner. In more extensive burns the problems to be confronted are the difficulties of immobilisation and nursing care. Experience will tell if these can be surmounted. In the majority of burns involving more than 30 per cent. of the body surface, the nursing

## TREATMENT OF BURNS

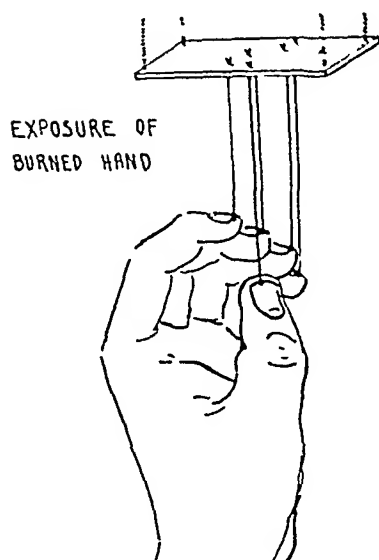


Fig. 10. A method of suspending the hand to allow exposure of burns.

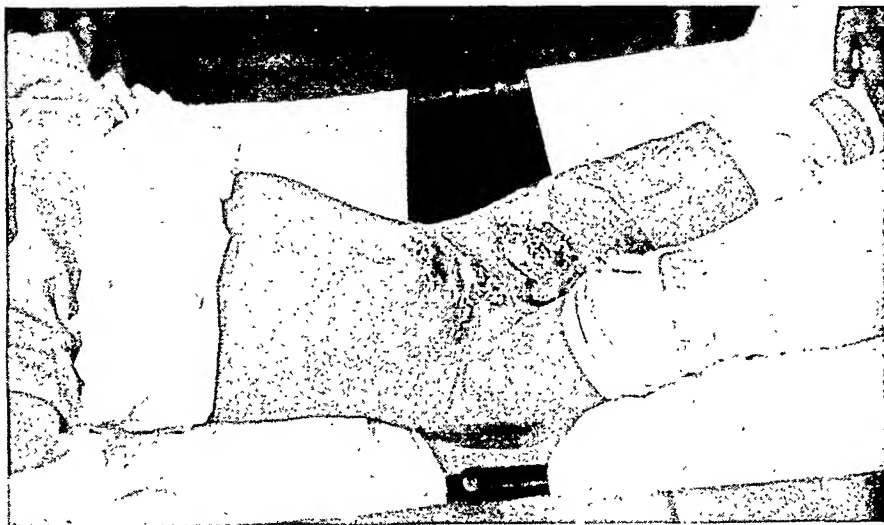


A



B

Fig 11. (a) Burns of the hand treated by suspension and exposure. (b) Fourteen days later.



A



B

Fig. 12. (a) Burns of the genitalia treated by exposure on a Bradford frame.  
(b) Fourteen days later.



Fig. 13. Burns of arm, chest, abdomen and leg treated by exposure.

care in the exposure method is extremely difficult and, therefore, the so-called pressure dressing method is preferred and suggested.

What are the results in deep burns? Further trials are required but the experience to date leads one to feel that deep burns can be treated by the exposure method with benefit until the time of surgical removal of the slough. Thereafter the problem is more of a purely plastic nature.

#### SUMMARY

The pathological physiology, bacteriology, pre-operative management and pressure dressing method of local care of burns are described. A preliminary report has also been given of burns which have occurred chiefly in babies and children treated systemically with penicillin and locally with penicillin powder, suspension, immobilization and exposure to the air of a surgical ward. The results are described and discussed.

#### IMPRESSIONS

The pressure dressing method of treating burns is most valuable. Many benefits, however, follow the treatment of burns by exposure but this method has obviously been on trial for too short a period to frame conclusions. The impressions gleaned, however, have been encouraging to the part played by body defences in the control of infections. The "humoral" factor has tended to be forgotten.

- (1) Superficial burns of moderate extent in any part of the body—the type which keeps the surgical wards occupied—respond favourably to suspension, immobilization and "air exposure."

- (2) A dry surface prevents multiplication of organisms and thus permits the body defences to accomplish healing by first intention, the penicillin powder being probably incorporated in the crust. An anti-bacterial powder, which does not antagonise the body's own defences, directed against both gram-positive and gram-negative organisms, would be a useful additional precautionary barrier.
- (3) For exposed burns, ward temperatures are probably more favourable to healing than body temperatures.
- (4) Deep burns can be treated initially in a similar fashion but within three weeks the slough must be excised and a skin graft applied.
- (5) If the exposure method is attempted, nursing care must be rigorous. This is most important in the first 48 hours.
- (6) It is too early to state the extent of burn which might be treated with safety by this method. It is possible to combine the exposure method with intravenous therapy. To assist in the nursing care, the pressure dressing method is suggested for all burns involving more than 30 per cent. of the body surface.
- (7) Benefits from pressure dressings are probably derived more from the immobilization and the absorption of moisture by the dressings and wool, than from the actual pressure.

I desire to express my thanks to Sister P. Robbie and to my resident, Dr. H. E. F. Dudley, Royal Edinburgh Hospital for Sick Children, without whose enthusiasm and application this study would not have been possible.

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it is subjected.\* If the irritation is slight, new bone is deposited and stress lines appear as in a skiagram of the head and neck of the femur. If the irritation is a little more pronounced, then clinically and radiologically the bone is described as being "sclerosed." This is seen as a thickening of the lamina dura round a tooth that has been slightly loose for years. If, however, the irritation is still more severe, then osteoclasts appear and the bone is resorbed. This response to mechanical irritation is seen radiographically as a thickening of the periodontal membrane of a loose tooth, and the same phenomenon of bone resorption is seen as a response to toxic irritation in the destruction of the bony alveolar crests where there is chronic marginal gingivitis, or round the apex of a tooth with a septic pulp canal.

It follows, therefore, that when a substantial fraction of the attachment of a tooth has been lost by bone resorption and proteolysis of the parodontal fibres as a result of the chronic marginal ulceration, a moment will come when the mechanical strain placed on the remaining part of the attachment of the tooth during mastication will also overstep the limit of physiological tolerance and set up further resorption of bone quite apart from any continuation of the sepsis at the gum margin. The process of destruction of tooth attachment then becomes quite automatic; for the moment that so much is lost that the strain on that which is left is too great, that remnant of attachment will also be progressively destroyed.

It is with just this predicament that the surgeon is faced when he attempts the conservative treatment of the teeth in an advanced case of pyorrhœa. He must deal with both the sepsis and the mechanical problem. His procedure must obviously be first to cure the ulceration of the subgingival epithelium in order to prevent the further toxic irritation of the subjacent bone and parodontal sling, and then to support the teeth or mitigate the masticatory strain on them in order to prevent the further mechanical irritation and destruction of the bone and of the parodontal ligament.

The first of these procedures, the elimination of the ulceration, will be carried out by excising the pockets, and instituting appropriate oral hygiene, that is, by getting rid of the subgingival epithelium altogether as far as possible. The second problem may perhaps be solved by grinding the occlusal contact, if it is only an odd tooth which is affected; but in any case of advanced parodontal breakdown where many teeth are affected, and perhaps lost teeth have to be replaced, the only solution will be to devise a parodontal splint.

The substance of this paper is therefore to describe any special modification of the ordinary operation of gingivectomy or of the after-treatment as applied to a case where a large proportion of the parodontal sling is destroyed, and then to discuss means of mitigating occlusal strain on the teeth by splinting.

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\* FISH, E. WILFRED (1948) *Surgical Pathology of the Mouth*, Sir Isaac Pitman and Sons, London.

There are cases where the whole pocket cannot for various reasons be excised; and there are patients who have lost so many teeth, or in whom those that are left are so loose, that however well they are splinted even their united strength is not enough to prevent each having to endure a strain so great that bone resorption continues and the parodontal fibres are progressively destroyed, so that the teeth loosen and are lost. Nevertheless, there are few cases which cannot be greatly helped and in whom the life of the remaining teeth, or most of them, cannot be usefully prolonged if the patient is sufficiently anxious to keep them.

### THE OPERATION

The surgical work is merely an extension and modification of the normal operation of gingivectomy followed by special supervision and instruction of the patient afterwards. It may no doubt be assumed that no one is likely to attempt to treat an advanced case until he is thoroughly experienced in the routine treatment of earlier manifestations of the disease\* so that only those special modifications of technique necessitated by the severity of the condition need to be described in any detail.

*The Selection of Cases* will depend on three factors. First of all it must be possible to eradicate the pockets, or, alternatively, to modify them in shape and extent so that the patient can completely explore what is left of them every day with a brush or a wood point. Secondly, the teeth must not be so loose that when united by a removable splint they will still be unstable under masticatory stress. Finally, the patient must be willing and anxious to go to the trouble involved in retaining his teeth.

The surgical problem arises simply from the contour of the surrounding tissues. In the case of the lower front teeth there is seldom any special difficulty. It is possible to cut away the whole pocket without any mechanical complication unless on the labial aspect the excision involves the reflection of the mucosa on to the lip, or, on the lingual side, on to the floor of the mouth.

When this occurs the subsequent pack gives rise temporarily to some painful, acute ulceration. This subsides when the pack is removed but it is difficult for the patient to keep the area well keratinised by friction afterwards. A very soft brush and much care and perseverance are the only prescription, but even then the prognosis is not good.

In the case of the upper front teeth and both upper and lower premolars, the limiting factor in excising the whole of a pocket is the contour of the bone. Fig. 2 shows the difficulty in the case of an upper incisor. If sufficient bone were removed to eliminate this pocket and at the same time restore some semblance of normal contour at the palatal gum margin, it is clear from the dotted line (A) that the whole shape of the palate would be altered and speech seriously affected. The only solution

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\* FISH, E. WILFRED (1944) *Parodontal Disease*, Eyre and Spottiswoode, London.

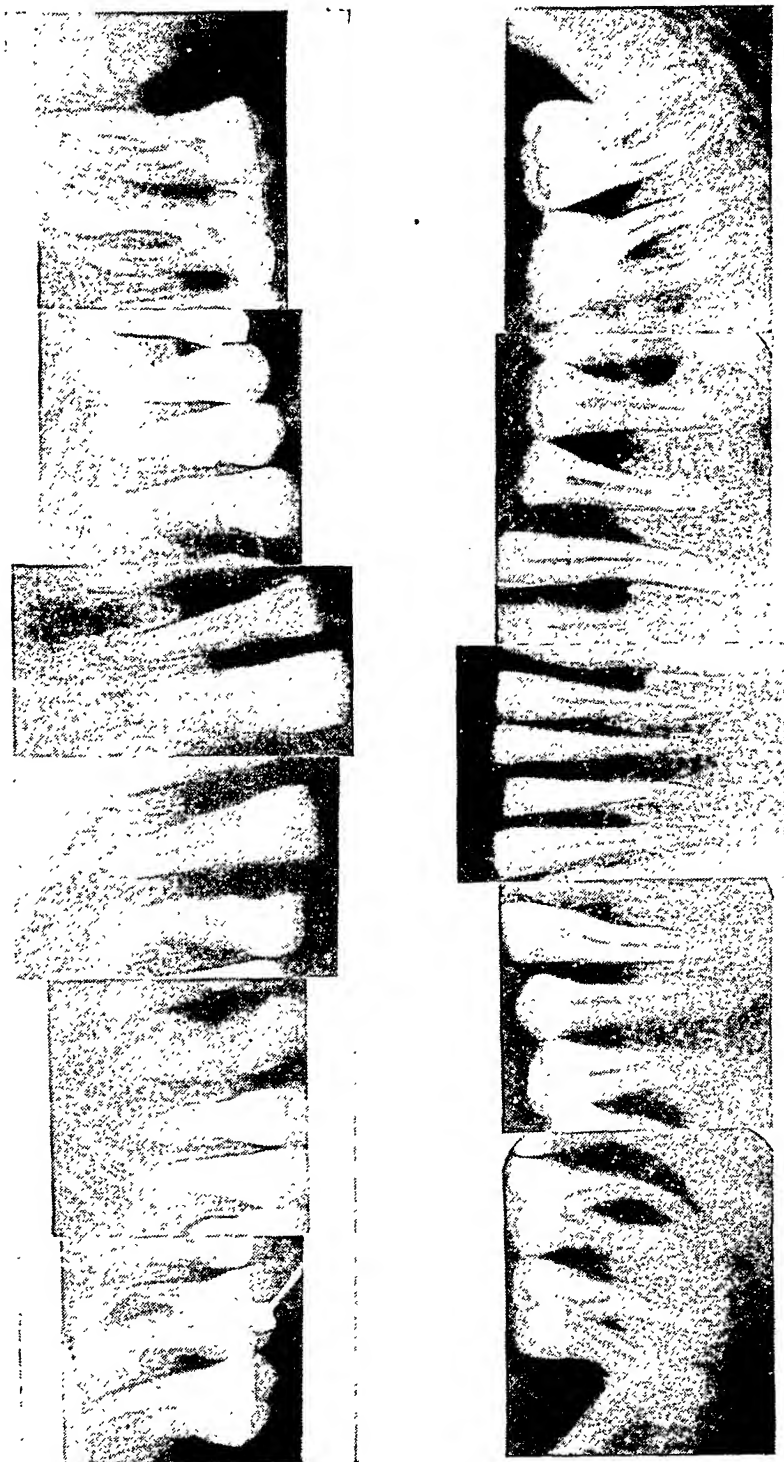


Fig. 1. An advanced case of periodontal disease (pyorrhœa profunda). There are especially deep pockets in relation to the first molars and the incisors. There is a probe in the pocket leading to an old paradontal abscess between the roots of the first right upper molar.



here is to be content with the best contour one can obtain without interfering with the bone; this is indicated by the unbroken line (B) in Fig. 2; unfortunately this solution imposes an additional duty on the patient to ensure that the bristles of the tooth-brush reach to the bottom of the open trough which now replaces the pocket.

The success that will attend the patient's efforts must, however, depend in a large measure on the efficiency with which the granulation tissue (Fig. 2(G)) is curetted away at the time of operation. This tissue is the remnant of the old parodontal abscess, which, by opening into the sulcus, caused the deep pocket, and it has since formed the bed of the subgingival ulcer. If merely the mucoperiosteum, which forms the fibrous wall of the pocket, be removed and this granulation tissue be left, the epithelium will rapidly cover it, but, having no firm fibrous foundation, will constantly and easily tear and the ulceration and the pocket will recur. So far, therefore, from the daily friction hardening the epithelium, it will tear it and reproduce the state of chronic ulceration for which the operation was originally performed. This is a very common cause of failure in the treatment of advanced pyorrhœa.

Even when the granulation tissue and debris are all removed the mechanical problem of applying friction to the epithelium at the bottom of a trough of this shape is not easily solved by the patient. The

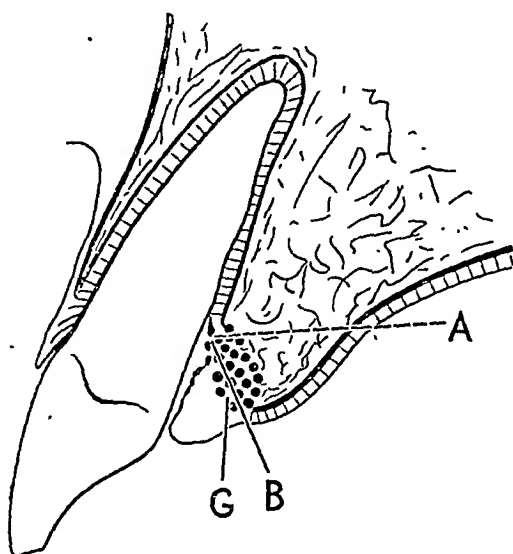


Fig. 2. Diagram to show the granulation tissue (G) replacing the bone and parodontal ligament on the lingual aspect of the root of an upper incisor. This must be removed at operation but the gingivectomy cannot follow the broken line (A) without destroying the contour of the palate. It must follow the line (B).

tooth-brush is the instrument of choice but everything depends on the method of applying it. The patient must be meticulously instructed. The brush should be held vertically and rotated on its long axis to sweep the bristles up into the trough. It is even possible to teach an enthusiastic patient to explore round the tooth under the gum with the flattened end of a balsa wood point, rather like lifting the cuticle of the nail. Obviously this is only possible round accessible teeth, generally at the front of the mouth. It is, however, an exercise which many women and some men will willingly practise rather than lose their front teeth, and many patients have kept their front teeth intact and free from sepsis by this means long after they had seemed hopelessly affected.

In the case of the molars both the operation and the after treatment may be complicated by the bifurcation of the roots. It is very common to find that a parodontal abscess has formed in this situation so that ultimately the pocket becomes an inaccessible labyrinth between the roots, even tunnelling through to emerge on the other side of the tooth (Fig. 1).

Generally such a tooth is quite loose and unable to contribute anything to the mechanical stability of the masticatory apparatus, whether it be as a natural tooth functioning independently or as a unit helping to support a splint. If it is reasonably firm, however, and the parodontal destruction has only just reached the bifurcation so that merely a depression appears after gingivectomy, the tooth-brush can often be made to reach the point at which the epithelium is actually attached and the tooth can be saved if assiduous and intelligent cooperation by the patient is forthcoming.

Whatever may be the mechanical complexity of the operation therefore, the extent to which it can usefully be carried is always governed by this necessity of leaving a state of affairs that will enable the patient to apply daily friction to the actual line of epithelial attachment all round each tooth, whether with a tooth-brush, a wood point, or by any other means.

If the ultimate line of attachment is not accessible to the patient, ulceration will persist, sepsis remain, and the tooth will eventually be lost.

*So far as the actual operation* itself is concerned, in any case where an extensive excision of tissue is contemplated in what must always be an extremely septic area, every precaution must be taken to avoid spreading the infection more deeply into the parodontal tissues. If this occurs the bacteria will set up a new parodontal abscess, which would at the best produce an even deeper pocket and might well lead to the loss of the tooth. An intramuscular injection of 500,000 units of crystalline penicillin before operation is an obvious precaution which should never be omitted, and this may be followed in very severe cases by further doses of penicillin for the next 24 to 48 hours. The loose tags of subgingival epithelium and granulation tissue between the teeth may be removed with fine, curved

The next consideration is the *management of the case after excision of the pockets* and healing has taken place. This can be summarised as careful scaling and constant supervision. It is imperative that long slender curettes should be available to remove every trace of tartar right down to the point of epithelial attachment; and where it has been necessary to leave bony alveolar walls at a higher level than the attachment, a pocket, or at least an open "trough," remains which can only be explored with a delicate instrument, especially between the teeth.

Similarly, the patient must be shown where such pocket remnants are situated, and, in addition to the ordinary "sawing" motion with the wood points, must be taught to work the flattened end of a balsa wood point down into this residual crevice every day to keep the epithelium hard and to prevent ulceration. The action is rather like working a manicure orange stick under the cuticle of the nail.

Above all, the patient must present for inspection at frequent short intervals, particularly at first, to be sure that no point on the gum margins is being missed in the rubbing. If it is, it will be clearly indicated by redness, ulceration and consequent tendency to bleed when disturbed by the scalers.

When such points are found the patient must be asked how they contrive the rubbing at that particular point, and some means must be devised to enable him to bring some kind of friction, either with brush or wood point, to bear on the neglected spot.

The visits should be once a month at first, then every two months, and then three; but these visits are not simply for inspection. At least "inspection" must include exploring with a fine scaler all round the epithelial attachment of each tooth to be sure that no trace of subgingival tartar has been overlooked or has re-formed. It is, of course, not a very tedious business since almost every pocket has been excised and no sulcus has much depth; still, it must be done and failure to carry out this procedure sedulously will mean a slow deterioration of the case, often hardly perceptible at first.

### THE MECHANICAL PROBLEM

The relief of mechanical stress on the teeth during mastication may be attempted in either of two ways. The occlusal contacts of the teeth may be ground so that the lateral component of the force, exerted by opposing teeth on each other, is minimised. Conversely, the teeth may be splinted together, either by a fixed splint or a removable one, so that they oppose their united strength to the masticatory stress.

The special disadvantages of the former method are that, in order to remove the lateral contacts of the front teeth, much tooth substance may have to be ground away, especially in cases of close bite which need relief most. Moreover, the food may still exert lateral pressures on the teeth so long as the temporo-mandibular joint permits lateral movements of the jaw. In an advanced case the individual teeth may not be able alone

to withstand masticatory stress, however modified, but may need mutual support. Finally, teeth may already be lost, and since their replacement will inevitably throw additional strain on those that remain, it seems essential that these remaining teeth should be strengthened in some way. It would seem to be imperative that they should be splinted or bound together so that they may withstand not only the normal strain, which in their weakened state threatens to be their undoing, but withstand also the additional strain of the prosthesis. Whatever place, therefore, the grinding-in of the teeth to restore balance to the occlusion may take as a prophylactic measure to prevent parodontal trauma in comparatively healthy mouths, in which all the teeth are present, it has no place in the treatment of advanced parodontal destruction; unless it be as a temporary measure, when an individual tooth may thereby be thrown out of occlusion, to rest it for a while until it grows back into occlusion again.

In advanced cases, therefore, some kind of splinting of the teeth seems to be inevitable. Some have sought a solution by fixing the teeth together with interlocking inlays; even 28 inlays in one mouth, each dovetailed into its neighbour, have been seen. If one inlay should come loose in such a case the replacement problem might be an anxious one, and the labour of this proceeding is not likely to commend it to many dental surgeons or their patients. On the other hand, a removable splint, savouring as it does of a partial denture, conjures up unhappy reflection.

Partial dentures have always been recognised as an exciting and continuing cause of parodontal destruction and many designs have been evolved to escape the devastating effect of their use. So consistently, however, does parodontal disease follow the use of partial dentures that some of us have at one time or another been constrained to advise our patients to contrive to manage with what few teeth remain to them, where there has been severe parodontal destruction, and to avoid partial dentures altogether; but unless the teeth, by virtue of long, sturdy roots, have still a good foundation in the bone, we have seen the destructive influence of masticatory trauma produce almost as sorry a spectacle as would have been brought about by a partial denture.

Consequently, for a long time, one was limited in parodontal treatment to such cases as presented with sufficient teeth for appearance, and for mastication, and sufficiently firmly planted to withstand occlusal stress without mutual support.

At length a case presented where there was some general parodontal breakdown, though it had not progressed as yet to any serious extent, except in the case of one upper central incisor where a parodontal abscess on the mesio-lingual aspect of the root had destroyed so many parodontal fibres that the tooth had moved out of the arch in the opposite direction, that is, labio-distally, as so often happens. The attachment of the remaining teeth, though still good, was somewhat weakened and the bite had "settled" to some small extent so that the misplaced central was held in its new unsightly position by the lower incisors.

The pockets were all cut away, the parodontal abscess excised and the epithelial attachments all well keratinised ; but this tooth was too ugly. Extraction and a bridge offered only a temporary respite for clearly what one central had done with average masticatory stress the other would quickly do when subjected to the abnormal strain of a fixed bridge. If, however, the bite were raised the tooth could be restored to its natural position ; but there again everyone knows that it is of no permanent value to raise the bite by inlays over the posterior teeth ; recurrence is certain. Moreover, there was always the risk that where one tooth had developed a parodontal abscess, another might follow suit unless the masticatory trauma were relieved all round.

It, therefore, only seemed possible to restore the good appearance of these otherwise beautiful teeth by raising the bite on the posteriors by a removable regulation appliance and regulating the errant central, as one would with a child ; but if this were done a retention appliance would have to be worn permanently, since the moment the regulation appliance was removed and the back teeth were allowed to come together, the lower incisors would push the upper central out again. Even if by some means the back teeth could be made to over-erupt, the parodontal attachment of all the teeth, having once proved incapable of sustaining the vertical height of the bite, could never be relied upon to do so again.

In the event the tooth was brought back into position again by an ordinary removable regulation appliance, and the device that was designed to retain this tooth was a gold casting covering the occlusal and lingual surfaces of all the upper teeth but not reaching the gum margins except at the two points where the palatal bar crossed (c.p. Fig. 4). This appliance took the biting strain imposed by the whole lower dental arch, every lower tooth being in occlusion with it. At the same time, by acting like the shoe on a horse's hoof, it prevented the upper arch from spreading under masticatory stress. The lower teeth were all exclusively biting on the gold, none of the upper teeth was in actual contact with a lower one ; and the new occlusal plane was considerably flattened in consequence, with elimination of lateral stress. No occlusal trauma could any longer fall on any particular one of the upper teeth alone so long as the patient was wearing this appliance ; each tooth had the support of its neighbours.

Finally, the tooth that had wandered from the arch and had been brought back into place, had an inlay set in its lingual surface. In this inlay a hole was drilled, and a pin, fixed in the splint, engaged the inlay and prevented any repetition of the movement of this tooth (Fig. 3). The inlay was set in the tooth before it was regulated, since after regulation a tooth is always a little tender until it has been fixed by the splint.

The splint was removable of course and had to be kept scrupulously clean as had also the teeth it covered ; but this patient had to devote some time to interdental friction in any case and her whole treatment depended on constant vigilance and unremitting care of her teeth and gums. Any recurrence of the gingivitis during the regulation of the tooth

which the tooth has moved ; and the movement is due to the loss of the restraining parodontal fibres. When many teeth are affected in this way a general spreading of the upper arch begins to occur, the bite slowly closes and unless the teeth can be supported by a splint at once the end is very near.

This applies particularly to cases in which most of the posterior teeth, either upper or lower, have been lost so that the whole weight of the bite is taken on the upper front teeth in a direction tending to expand the arch ; yet if these teeth are united during mastication by a splint which fits round each so closely that the united strength of them all is presented to the onslaught of the lower arch they may survive unmoved for years. The prospect is particularly bright if it is the lower molars which are lost and most of the upper teeth are present, for the upper splint will take attachment from the back teeth as well as uniting the front ones.

The stabilising principle of developing the united resistance of the teeth to excessive movement, by covering their occlusal and lingual surfaces with a removable gold casting interposed between the teeth themselves and those of the opposing jaw, is one which, as I have said, can be extended to the construction of almost all partial prostheses. The general principle is that the " plate " is fitted to the occlusal surfaces of all the teeth rather than to the soft alveolar and palatal tissue, and any teeth that are missing are replaced by plastic substitutes which hang down from the plate to touch the gum instead of rising up out of a plate which is fitted to the gum. Figs. 4, 5 and 6 may serve to illustrate the principle where there are a number of teeth left.

Where there are only front teeth the same principle is applied. The casting takes occlusal support from each canine by covering the distal slope of the biting edge, possibly modified a little in shape by grinding. Occlusal support on the incisors must be obtained where necessary from inlays such as the one illustrated in Fig. 3 ; but when there are plenty of back teeth this additional support is not necessary unless an incisor has been moved back into line, and then the inlay is intended to retain the tooth in position rather than to give occlusal support, though of course it does both.

It is not possible to discuss at length individual types of design, but, where for example the posterior maxillary teeth are all missing on one side but not on the other, it is necessary to make a saddle for that side. This saddle is connected across the palate to the splint on the other side with the usual palatal bar. Provided the impression was a sectional composition type, compensated over the soft edentulous part of the maxilla, the result is very satisfactory and any subsequent resorption is compensated no doubt by a slight gradual movement of the teeth. At any rate such appliances do not as a rule develop a rock or need relining, though one would not expect to succeed with any other kind of impression.

Even quite loose teeth, permitting considerable lateral movement, will prove most valuable in providing vertical support for a splint, and their

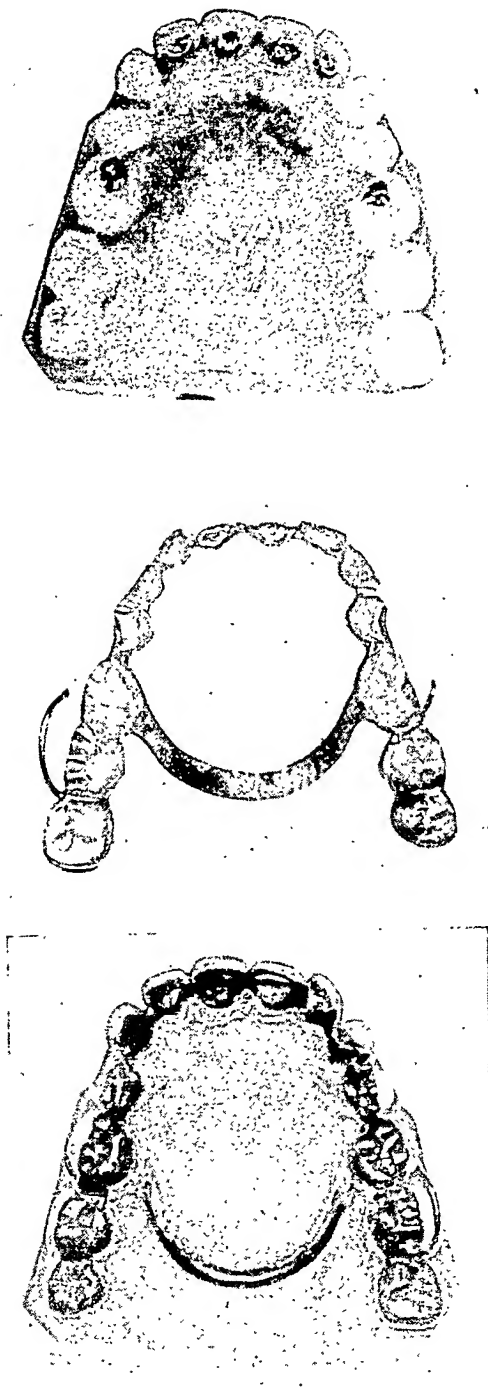


Fig. 4. A splint of a type designed to give mutual support to the teeth, and to prevent their individual displacement or, as in this case, to retain the four upper incisors which have been retracted. There are pins on the splint which engage holes in inlays set in the retracted teeth. The patient was aged 43 and had had a complete gingivectomy.

ADVANCED PARODONTAL DISEASE

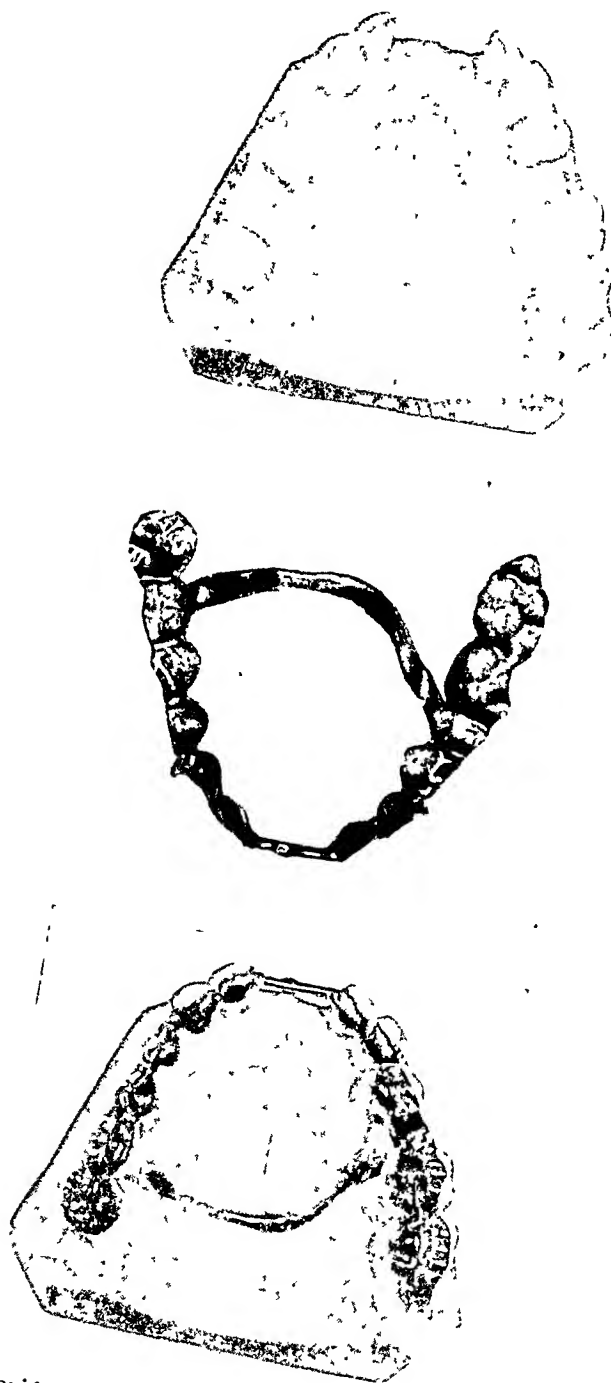


Fig. 5. A splint to provide mutual support to the remaining upper teeth and to replace those that are lost.



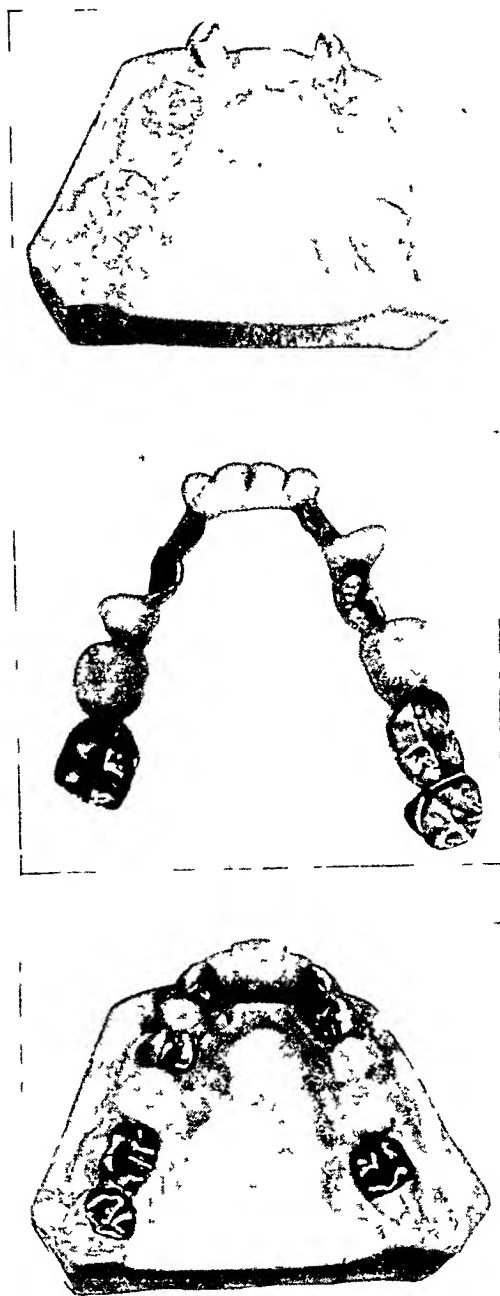


Fig. 6. A splint to afford mutual support to the remaining lower teeth and to replace those that are lost. In both Figs. 5 and 6 the "plate" covers the occlusal surface of the teeth and does not rest on the mucosa. The plastic teeth hang down from the "plate" to rest on the edentulous alveolus and the plate itself is completely tooth-borne.

# THE DEVELOPMENT OF MICTURITION CONTROL WITH SPECIAL REFERENCE TO ENURESIS

Hunterian Lecture delivered at the Royal College of Surgeons of England

on

21st February, 1949

by

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I HAVE TO REPORT no startling or new romantic surgical manœuvre, but I hope that what follows may perhaps act as a shaft of light on the dank, drab and dreary picture of the child with urinary incontinence and that others may be stimulated to pursue some of the outstanding problems.

The physiology of micturition has never been adequately explained in man. Our present conception of the mechanism is still based primarily on the work of Denny Brown and Robertson, at the National Hospital for Nervous Diseases in the early 1930s. Their findings were based solely on cystometric observations upon three adults, of whom two were the authors themselves. The classic work of Barrington (1933) was based on cat experiments and sought to elucidate and locate various spinal and cerebral micturition centres. He was unable to separate sensory and motor pathways.

The most recent review of the various aspects of the encephalic control of micturition is by George Clarke (1945). He sums up: "Denny Brown and his co-workers maintain that the cortical control of the bladder consists in the inhibition of spinal reflexes. Other workers have reported relaxation of the bladder upon stimulation of higher centres and yet others have reported detrusor activity from cortical stimulation." In conclusion he writes: "The experimental evidence on the encephalic control of the bladder is so contradictory that a theoretical explanation is impossible until further work is available."

For this presentation I am, however, accepting the Denny Brown concept of inhibition by the higher centres but at the same time I believe that the behaviour of the child's bladder would also "fit-in" with the existence of a motor micturition stimulus from the cortex. I believe that there is such a stimulus.

The human child cannot be used as an experimental animal except in a very limited way, and the investigations upon which my observations have been based have been limited by the overriding compulsion to bring one's curiosity within the limits of necessity.

McLellan (1939) in his book *The Neurogenic Bladder*, and Langworthy, Kolb and Lewis (1940) in their book *The Physiology of Micturition*, and Mr. E. W. Riches (1943) in his Presidential Address to the Section of Urology at the Royal Society of Medicine, have all derived much of their information from cystometry. My findings, however,

included mental defectives. Many of these so-called "disorders of function" have, most likely, an organic pathology. A "disorder of function" is not by any means synonymous with psychopathology.

The lay conception of urinary incontinence in children usually falls into one of two categories. There are those who believe that the child cannot help it and they hope that he "will grow out of it." Many of these parents make little effort to rid the child of his crippling burden. The second view (often that of a father) holds that it is due to lack of discipline and the consequent treatment may or may not do good. In hospital enuretic children appear in and around all departments. Their parents are often despondent, confused and sometimes desperate. The number of defaulters in any series is big because the parents tire of attending when there is no dramatic improvement.

All too often, the attitude of school teachers is deplorable and many maintain that even day frequency requires stern discipline. In his very excellent book *Enuresis*, Dr. R. J. Batty of Blackpool (1948) repeats the question, "Why does the statue of Liberty stand in New York Harbour surrounded by water?" The answer is she had her hand up and the teacher did not see it! During my investigations I have come up against several school teachers in the London area who have been aggressively unco-operative, and any attempt to deal with them leads to victimisation of the child. In one case a headmistress threatened the boy's mother that she would not recommend him for a scholarship because we had complained about the form master's bullying.

So much for the background. It is necessary to study this in order that there may be kept in mind the very many facets of the problem of micturition control.

### THE CYSTOMETRIC INVESTIGATION

The original purpose of this investigation was to determine the value, if any, of cystometry in relation to incontinence in the child.

It is necessary first to outline the normal or expected pattern. Cystometry is the simple measurement of intravesical pressure following the slow filling of the bladder through a urethral catheter. A simple manometer (Fig. 2) is used and to avoid a double long column of fluid, the fluid from the reservoir is allowed to run through a small catheter into the top of the manometer. The fluid used is 1·10,000 warm potassium permanganate. The rate of flow is about 60 drops a minute to start with and, broadly, one keeps the rate at that, but it can be speeded up when the bladder contains three or four ounces. The basal pressure of fluid is recorded after each unit of 20 mls. have run in and any contractions of the bladder producing a rise of more than 2 cms. pressure are noted. Respiratory and minor body movements do not in any way affect the readings.

In about 150 observations on children between the ages of 2½ and 14 there has never been any suspicion of infection following cystometry.

The selection of the catheter is important, a number 4 or 5 soft rubber catheter is used and it is essential to make sure that the shaft proximal to the eye has a reasonable aperture ; some of them have a thick isthmus just proximal to the eye. It is lubricated with 2 per cent. amethocaine jelly and this often gives sufficient anæsthesia for the cystoscope to be slipped in at the end of the examination. Only twice have I had to give up the cystometry because the child cried or was resistant and, once the catheter has been put in—very gently—there is no discomfort. It is essential to eject from the room all over-affectionate observers and assistants who may make useless “small talk” with the child. I have come to respect most highly the ability of these children to be accurate observers and most tolerant co-operators.

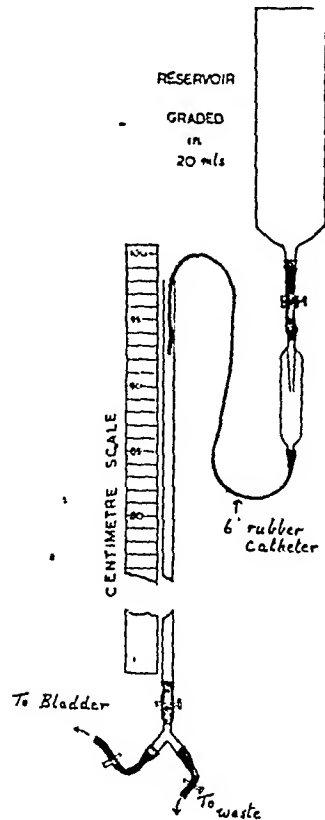
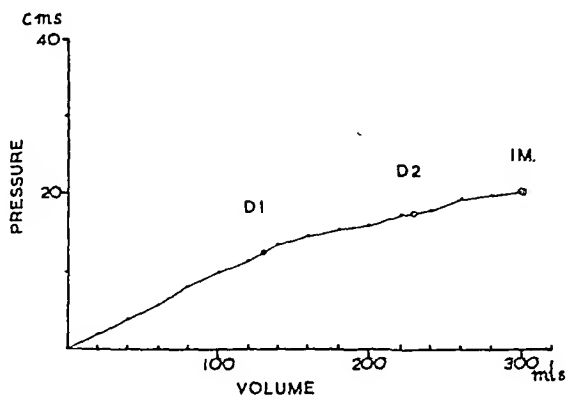


Fig. 2.

*What do we want to find out?*

Charts are plotted uniformly with the pressure ordinate five times the volume abscissa (Fig. 3).



NORMAL CYSTOMETRY.

Fig. 3.

First, on the sensory side, one wants to know whether there is a sensation of filling, whether, if the bladder contracts, that contraction is felt and whether during filling the child has the normal recurrent points of desire to void. This desire can normally be overcome by deep breathing and should be *unaccompanied* by any rise of pressure. There are two such points in the normal adult: one at about 100 mls. another at 200 mls. and the third is intense and micturition is usually imperative at this point, *but still there is no rise of pressure*. These "desires" to void are labelled "D."

In the infant, during its first few months and probably until the age of one year, micturition is automatic. The bladder fills up, perhaps to half-an-ounce and without previous contraction empties itself with considerable force over whoever or whatever happens to be present (Fig. 4 (a)).

At the age of three months the urinary output is approximately 12 ounces in 24 hours, and there are very few babies who are wet less than 12 times in 24 hours. Capacity then is very small.

During the second year, suppression of the initial contraction takes place and it is possible that the cerebral centre responsible is mid-brain or even higher. As the months go by the second, third and subsequent attempts of the bladder to contract are suppressed (Fig 4 (b)). Also, as the months and years go by the bladder increases in actual size and, therefore, in capacity (Fig. 5). The two factors—the development of

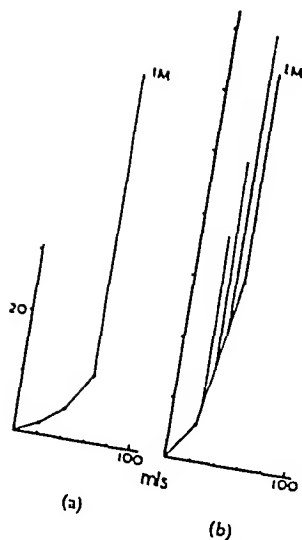


Fig. 4.

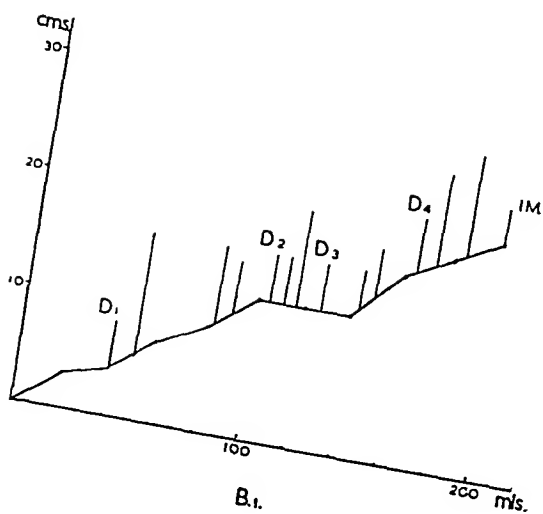


Fig. 5.

function and the development of form—lead to the establishment of the normal bladder and its control at the age of three or four (Fig. 6).

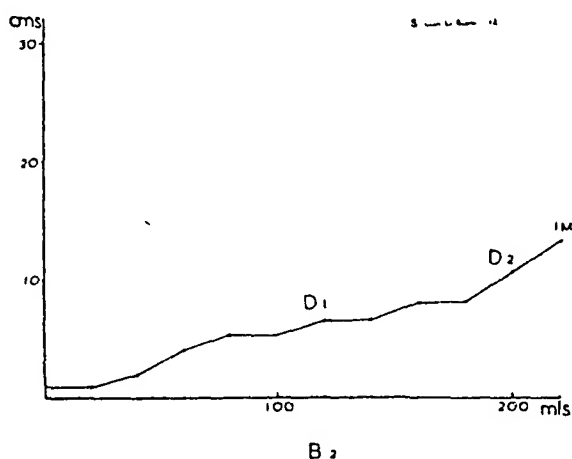


Fig. 6.

Progress through these stages can be shown cystometrically and it is convenient to label the cystometric patterns (Fig. 7).

#### CYSTOMETRIC TYPES

- A 1. AUTOMATIC — Infantile
- A 2. HIGH TENSION UNINHIBITED
- B 1. LOW TENSION UNINHIBITED
- B 2. LOW TENSION INHIBITED

Fig. 7.

Two types have uninhibited or, more correctly, imperfectly inhibited contractions which do not lead to the passage of urine when the catheter is in position. The A1 type is the automatic infant bladder with high tension and small capacity.

The B2 is the low tension normal adult pattern. A2 and B1 represent the intermediate stages of development, with a difference of capacity mainly, although the pressures and the base tension are in fact higher in the A2 type. A capacity of 100 mls. is taken as the arbitrary division between the two.

The uninhibited contractions are entirely involuntary and are often bi-phasic—the first part being slow and not reaching consciousness: a slight fall then occurs, followed by a faster rise and perception occurs during the intermediate fall. I think the second phase probably represents a motor impulse from the cortex: the pattern is quite constant.

asleep during the cystometry and Fig. 8 is the second record. He was awakened by the final contraction.

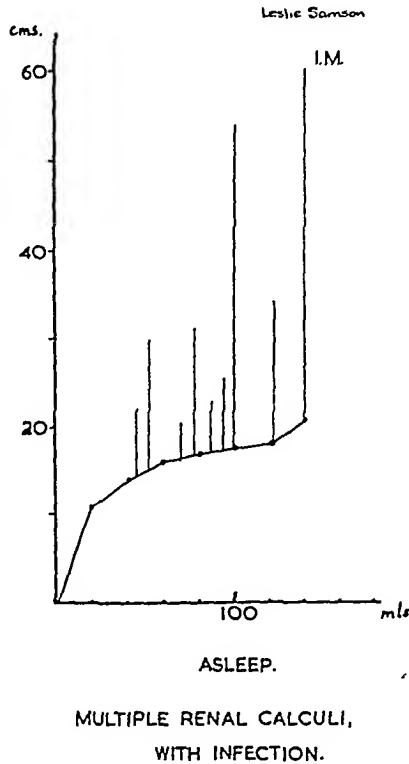


Fig. 9.

It is not possible, as I have said, to use the child as an experimental model and, therefore, the repetition of cystometry at various stages of treatment is not really feasible. I have, however, been able to obtain a second reading in a few cases and Fig. 10 shows the consistency of pattern on different occasions in the same child without treatment. This can be compared with a similarly treated case (Fig. 29).

#### THE CLINICAL AND CYSTOMETRIC REVIEW

This is taken from my personal records of 218 unselected cases, each one having been referred to me direct from a general practitioner or from a hospital department, *not because the child had organic urinary disease, but purely on account of enuresis*. Over 90 per cent. had already been treated, some for years. Not a few had already had psychotherapy.

It is quite extraordinary that even in the presence of gross known organic disease, a child can still be labelled "enuretic" and one's



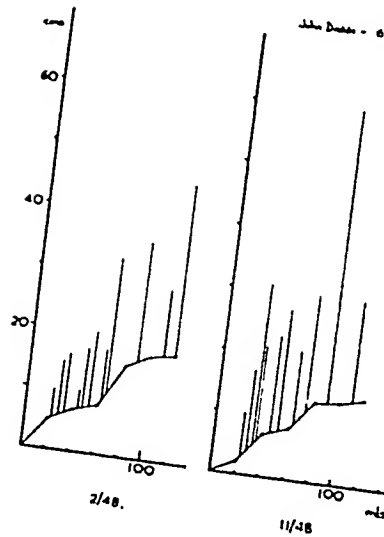


Fig. 10.

impression is that hospital staffs are far too complacent in their attitude. Very often they do not even know that their young patients are incontinent.

I would like to refer again to the British Medical Association and Magistrates' Report, paragraph 17, which makes this remarkable statement: "The child should be examined by a doctor and sometimes the cure of a persistent infection of the urinary tract is necessary." The burden of responsibility which is thus placed on that doctor's shoulders is very great.

### THE CLINICAL HISTORY

There are, of course, many factors to be taken into consideration when interviewing the parents. The urologist should take the history himself—a full *pædiatric* history, for which he must be trained. It is essential to know if the baby or child has, in fact, ever been dry for a day, for an hour or even for half an hour. It is also necessary to go into the details of the birth—whether there was asphyxia or a forceps delivery. In one of my cases the child was born with the cord round his neck and he has almost unnoticeable hemiparesis.

### THE SYMPTOMATIC CLASSIFICATION

In direct regard to the incontinence, the cases fall into various clear-cut categories (Fig. 11). There is a total of 218 cases: three cases of  $2\frac{1}{2}$  years old all became normal in three months and have been excluded. Gross organic urinary tract lesions were present in 21 cases, and these will be discussed later; there were included in this organic group only those cases about which there can be no dispute as to the cause of the incontinence. In the functional group I found 42 cases (20 per cent.) with

## PHYSICAL

GROSS ORGANIC DISEASE OF URINARY TRACT	..	..	21	10%
OTHER ORGANIC DISEASE	..	..	8	4%
Cerebral Palsy, Petit Mal, etc.				

## "FUNCTIONAL"

WITH PAST OR PRESENT URINARY TRACT LESION	..	42	20%
NO PHYSICAL ABNORMALITY FOUND..	..	132	
THREADWORMS	..	12	66%
TOTAL FOR ANALYSIS	..	<u>215</u>	
TOO YOUNG TO BE CONSIDERED ABNORMAL	..	3	

CAUSE ORGANIC 14%

CAUSE UNKNOWN 86%

TOTAL UROPATHOLOGY	..	30%
ORGANIC AND CONTRIBUTORY LESIONS	..	40%

Fig. 11.

urinary tract lesions, probably the result of the incontinence, rather than the primary cause, but all needing treatment. Winsbury-White (1944) found that 70 per cent. had urinary pathology but I have not included posterior urethritis and trigonitis as it has in fact been impossible to urethroscope more than a small percentage. These lesions which I have included could all have been spotted by a physician or a surgeon without any optical apparatus other than that provided by nature or by the National Health Service.

In this whole group are six day wetters—no night symptoms and probably all psychological in origin. Incidentally, all but one cleared up with simple treatment without resort to a psychiatrist, and they constitute a different problem. The sixth one is unimproved, except while in hospital, and my psychiatric colleagues tell me it is because her mother still wants her as a baby!

It is upon the so-called functional group that I wish to dwell. There are 186 cases and they all fit most clearly into a symptomatic pattern.

STAGE I. These children at the time of the first examination by me had never had a single dry night. This is a dreadful picture, the child age four, five, six or even more with never one dry night. There is no question of the mother having forgotten the odd dry night—which would have been an occasion for rejoicing. All of them had day symptoms, very often wetting, sometimes frequency more often than  $1\frac{1}{2}$  hours, and almost always urgency. If the school teacher won't let such a child leave the room, it is little wonder that the child becomes a rebel and disturbed in his or her social relationships.

STAGE II. The same state of affairs exists here except that there has been an occasional dry night, thus establishing at least that the trouble was not a fistula or ectopic ureter. Curiously, in none of these had any remissions been longer than a week. Day symptoms are as in STAGE I.

# HUNTERIAN LECTURE

STAGE III. Here there were no day symptoms and remissions were all under one month, most of them four or five successive nights.

STAGE IV. No day symptoms. Night remissions over a month.

STAGE V. This is introduced really as a means of describing progress ; by this group is meant one or two wet nights a term. Cases of this type rarely seek treatment.

STAGE VI. This is the normal bladder function.

These stages represent the normal bladder behaviour at progressive ages (Fig. 12). Thus, *Stage I* represents the behaviour of the bladder during the first year. *Stage II* represents behaviour during the second year of life, when the child is quite unreliable during the day time " but if I can catch him " (to use the mother's words), " he can be kept dry." During the third year the normal child is perfectly reliable during the day

STAGE	SYMPTOM GROUP	BLADDER AGE	CYSTO-METRY
I	LIFELONG NIGHT WETTING. NEVER HAD A DRY ONE. DAY SYMPTOMS.	0—1	A 1
II	LIFELONG NIGHT WETTING. OCCASIONAL DRY ONE. DAY SYMPTOMS.	1—2	A 2
III	LIFELONG NIGHT WETTING. REMISSIONS UP TO A MONTH. DAY NORMAL.	2—3	B 1
IV	REMISSIONS OVER ONE MONTH. DAY NORMAL.	3+	B 2
V	VERY OCCASIONAL WET NIGHT.		
VI	NORMAL.		
VII	ONSET TYPE.		MIXED

Fig. 12.

with a frequency of 2-3 hours and although a more forward child is also reliable at night, the average child does not achieve reliable night control before the end of its third year.

Between the age of three and four the child may still have odd lapses on party nights or on festive occasions or when he is ill. Even after the age of four many children have an occasional wet bed.

We have, therefore, already a progressive developmental pattern in our *symptomatic* analysis.

Fig. 13 also shows the average ages in investigated groups. These only are averages and there are wide variations, but these figures again bear out the developmental pattern :—

STAGE	No.		AVERAGE AGE
I	41	22%	6.4 years
II	61	32%	7 years
III	22	12%	9.1 years
IV	7	4%	9.3 years
VII	49	26.5%	8 years
Day Only	6	3.5%	8.7 years
<hr/> 186 <hr/>			

#### FUNCTIONAL CASES

Fig. 13.

It will be noticed that 54 per cent. of these lifelong wetters have day symptoms, so we should perhaps beware of the term “nocturnal enuresis.” Twenty-two per cent. had never had a single dry night with an average age of 6.4 years.

We can, therefore, give an enuretic child a “Bladder Age” according to his symptoms.

**The Onset Type—STAGE VII.** Comprises those children who have developed and maintained normal bladder control, some of them a year or more behind schedule, and who have subsequently reverted to an earlier type of bladder function. The reason for this reversion to incontinence is uncertain, but some 36 per cent. have had precipitating organic factors or associated factors which may well have been causative. In only two cases was there any definite psychological trauma. After the onset the intensity of the disability may increase rapidly and again we find that all these Stage VII cases can be classified into our symptom stages.

Eighteen per cent. of the “Onset Type” had occurred following some incident which may have produced cerebral damage by hæmorrhage or congestion (Fig. 14). Fig. 15 is the cystometrogram of a boy of five who developed enuresis immediately after sunstroke. Nearly two years’ treatment of all sorts has been completely ineffective. Most of the “Onset” cases commence their symptoms at nursery school age; very few are over the age of five (Fig. 16).

The bulk since onset had had occasional dry nights and had day symptoms and were like Stage II. The rest were like Stage III. We

# HUNTERIAN LECTURE

STAGE VII

ONSET TYPE

PRESENT SYMPTOMS STAGE II=35 CASES  
PRESENT SYMPTOMS STAGE III=14 CASES

49 CASES  
26.5%

ONSET FACTORS

SUNSTROKE	1
PERTUSSIS	2
BOMBS	2
POST-OPERATIVE	3
JAUNDICE	1
	18%

ELEVEN OTHERS HAD ASSOCIATED FACTORS

THREADWORMS	3
INFECTION	2
ADHESIONS	4
PSYCH. TRAUMA	2
	22%

Fig. 14.

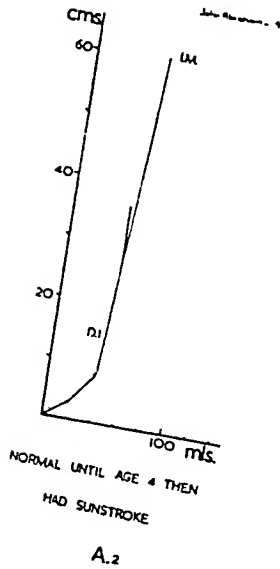
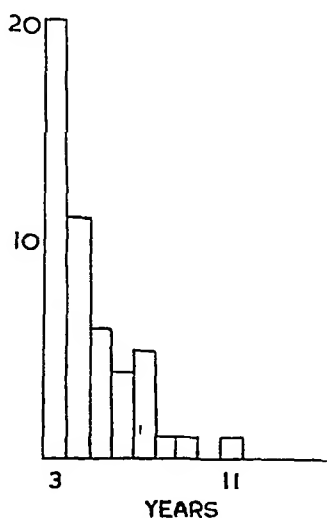


Fig. 15.

can, therefore, describe all these "Onset" cases as VII/II and VII/III, etc., using the symptom stage classification at initial and subsequent examinations. (*e.g.*, *Stage VII/III* would indicate that the child had become dry and reverted but now had no day symptoms with dry intervals at night up to one month.)

## STAGE VII



## AGE OF ONSET

Fig. 16.

Enuresis, therefore, in this major functional group becomes to be regarded either as a clear developmental arrest, that is, *Stages I to V*, or as a reversion problem—*Stage VII*. Perhaps this is too simple a way out. Children vary enormously in the development of cortical function on the motor side, and the micturition centres may well lie here. Some children can tie up their shoes at three years old; others make heavy weather of their knots at 33! Some can play the violin, others can scarcely saw a piece of wood. Some take up ophthalmology others orthopaedics.

McGraw (1943) in her fascinating book "The Neuromuscular Maturation of the Human Infant" calls attention to the normal ebb and flow of the tide of toilet control which occurs during the first three years of life. This maturation is not a straight line of progress but exhibits two and sometimes three periods of decline as other phases of the child's

## GROSS ORGANIC DISEASE OF THE URINARY TRACT

## CONSIDERED CAUSATIVE

PHIMOSIS	1
URETHRAL VALVE	1
URETHRAL POLYPS	3
PERSISTENT INFECTION	2
IMPERFORATE HYMEN	1
PELVIC KIDNEY	1
MYXOMA OF BLADDER	1

RETENTION WITH OVERFLOW  
BLADDER NECK OBSTRUCTION

MENINGOCOELE	6
IDIOPATHIC	2
MEATAL STENOSIS	3

TOTAL	21 = 10%
-------	----------

AGE RANGE 4-12 YEARS

AVERAGE AGE 9.5

Fig. 18.

Like the members of a famous club, there are two classes in this group—those who can't pass their water and those who can't hold it.

I want to underline the fact that these lesions were revealed in routine investigation of incontinence, called by the referring doctor, "Enuresis." A few examples are given below :—

CASE NO. 1. *A boy aged eight.* A lifelong night wetter (*Stage III*) found to have a pelvic kidney floating on his bladder. Right nephrectomy by Mr. Twistington Higgins cured his enuresis.

CASE NO. 2. *A boy aged six.* Always unreliable but enuresis became very troublesome after an operation for squint. On this account his urine was tested and found to contain albumen. He had a residual urine of 20 ounces and gross upper and lower tract dilatation. Blood urea 85 mgms. Three months after the resection of a V-wedge from the bladder neck he was dry day and night and had a residual of 1½ ounces (Fig. 19).

CASE NO. 3. *A girl aged five.* Dribbling incontinence all her life (*Stage I* type). Found to have a distended bladder and nearly a pint of residual urine. Following a bladder neck V-wedge resection her residual was reduced to less than two ounces and she was dry.

CASE NO. 4. *A girl aged six.* Intermittent incontinence and pyuria. She fitted into no typical symptom group, which led one to think of organic disease. Two urethras were found, both apertures looking normal. There were two bladders both capable of being cystoscoped. The posterior one had a gaping left ureteric orifice and the supernumerary ureter, pelvis and upper pole of the left kidney were removed. The redundant bladder cannot, of course, be removed without endangering control. She is now dry (Figs. 20(a) and 20(b)).

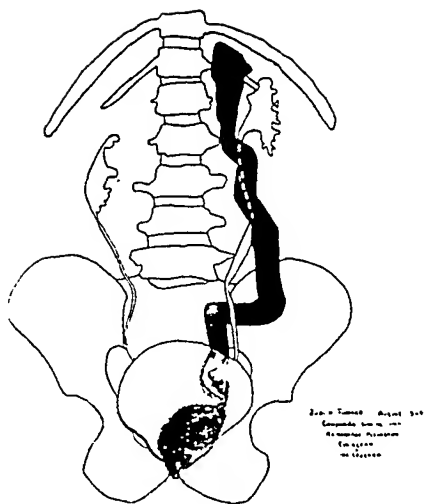


Fig. 20 (a).



Fig. 20 (b).

(Fig. 21). Her mother's description is most impressive. Before surgery the child was saturated day and night and used three or four pairs of knickers a day and many napkins. One month after the resection the mother rejoiced that one pair of knickers did the whole day, and two months after, the child requires one pair a week and is absolutely dry and reliable by day up to three hours in spite of parties. She has already had one dry night, and this is after five years' misery. She has started school.

CASE No. 6. This girl aged nine has a mild hydrocephalus and she is waiting for a V-wedge resection. Fig. 22 shows the formation of a diverticulæ in the neurogenic bladder, in the second case referred to under this type.

All these children have extensive saddle anæsthesia, and the two with systolic bladders also have involvement of their leg muscles so that they are sitting about more in their puddles, which makes worse the ulceration, infection and bladder irritability.

#### OTHER ORGANIC DISEASE CONSIDERED CAUSATIVE OF INCONTINENCE

Analysis of these is shown in Fig. 23. There were four cerebral injuries, three from birth and one toxic. I am sure many more enuretics than we realise owe their disability to similar cerebral causes.

There were four cases of Petit Mal. Some of the mals are so petits that they might well be missed unless the specific questions are asked in the history taking. Fig. 24 is the cystometrogram of one pyknoleptic, a boy of nine. I believe that this recording is of very great significance. He was having scores of attacks each day. He had four attacks in the





Fig. 21.



Fig. 22.

half an hour during the examination ; each lasted less than three seconds and was accompanied by a violent detrusor contraction followed by complete relaxation. These contractions were much more rapid than the so-called vesicogenic uninhibited contractions. Similar high tension waves have been found in other petit mal cases and I feel sure that we should regard such a finding always as demanding electro-encephalography and further investigation. This boy did not respond to tridione.

#### UROPATHOLOGICAL FACTORS NOT CONSIDERED CAUSATIVE OF INCONTINENCE

In considering the uropathological factors in the "functional" group, I feel that these are not causative but contributory (Fig. 25). It is seen that the greater number occurred in the more primitive and severe stage groups, suggesting that the lesions in the urinary tract are, most probably, the result of the incontinence. To be bathed in decomposing urine, day in and day out, night in and night out, is a pretty certain guarantee of developing ammonia dermatitis, and its train of pathology from meatal stenosis to melancholia. When the child lies all night in bed clothes that are wringing wet, it is little wonder that she develops an ascending infection.

Although some of the "Onset" Type cases (*Stage VII*) developed as the result of infection, cure of the primary lesions has by no means always led to the cure of the enuresis. It is, however, significant that 22 per cent. of the functional group (42 cases) had urinary tract lesions requiring treatment. This is another line under paragraph 17 of the Magistrates' (1948)

# OTHER ORGANIC DISEASE CONSIDERED CAUSATIVE

PETIT MAL	4
SPASTIC PARESIS	3
POST-ENCEPHALITIS	1
TOTAL	<u>8</u> = 4%

Note.

PROBABLE CAUSATIVE ORGANIC FACTOR,  
STAGE VII CASES—II, i.e. 5%

Fig. 23.

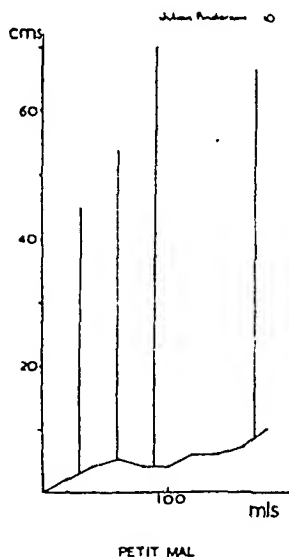


Fig. 24.

recommendation, "That the child should be examined by a doctor." If we include infestation with threadworms we have 29 per cent. requiring treatment.

## The Treatment of Neurological Disorders of the Bladder in the Child

Reference has been made to the treatment of the meningocoele paralytic bladder. Children with meningocoeles should have the urinary tract

Fig. 27 shows the percentage of cases in each group which remain unaltered after three months' attendance and that normally represents an attendance of once a month. Here again will be seen the age progress, improvement being easier to achieve in the more primitive groups. In the *Stage VII* cases (Fig. 28) it will be seen that there is a similar reasonable improvement in three months. It is difficult to say cases are cured until they have been followed up for a year, but out of 158 followed for three months, it will be seen from Figs. 26 and 28 that 20 per cent. had achieved remissions of longer than a month and 68 per cent. were greatly improved : that is, they had moved up at least one stage.

### PROGRESS—1

		PROGRESS STAGE 3/12 LATER					
STAGE	NO.	I	II	III	IV	V	VI
I	40	7	I	30	2	—	—
II	52	—	17	27	3	4	I
III	18	—	—	10	4	3	I
IV	6	—	—	—	4	2	—
DAY WETTERS	6	—	—	—	—	—	4

Fig. 26.

### PROGRESS—2

#### UNCHANGED AFTER 3/12 TREATMENT

STAGE I	10%
II	33%
III & IV	55%
VII	30%

TOTAL "CURE" RATE AT 3/12=161 CASES

STAGES V & VI

FUNCTIONAL GROUP 13%

Fig. 27.

### PROGRESS—3

STAGE VIII	
OF 36 CASES FOLLOWED 3/12	
42%	15 IMPROVED
12%	4 GREATLY IMPROVED
16%	6 "CURED"
30%	11 I.S.Q.

Fig. 28.

### THERAPEUTICS

Of drugs there is little to say. The time-honoured Belladonna has singularly little effect, although one would expect that it might suppress uninhibited contractions. This it *would* do but it also produces cerebral excitation which will not help any cortical arrhythmia which may be

number of resistant cases, too few for review, I feel sure that there has been improvement due to the use of this drug. If its use does in fact diminish the congestion of the verumontanum then it is easy to see why it should work.

In girls, especially between the ages of nine and 13, it is common to find a mild vaginitis without any specific causative organisms. Such cases should be treated with Stilboestrol (0.5 mgms.-1 mgm. at night for two weeks) and it has been found in a number of cases that this alone has cured the enuresis.

Anti-histamine drugs, nicotinic acid and hyoscine have not been found to give any benefit.

Psychological treatment has been singularly disappointing, and a number of children I have seen have developed faecal incontinence—encopresis, a word not in general use—as well while under psychological treatment. I am not competent to say whether such a development emphasises the need for more psychotherapy or merely indicates the normal child-like disgust at being shut up with a box of sand and a pail of water to play under observation twice a week. Just as we may expect to find uropathology in a child who has lain in a bath of ammonia, so may we expect him or her to develop some psychological aberration.

It may be wondered with all these doubtful remedies how one can claim about a 90 per cent. case improvement in three months. The method is very simple and depends on being accurately explained to the mother. It is quite useless to tell the child that he or she must wait when the bladder has already given the signal "full." Think again of the statue of Liberty. To put it very simply we must avoid all day the afferent impulse and the child is sent to pass its water every quarter of an hour, then every half an hour and so on, increasing to two hours over a period of a few days and this must be kept up "by the clock." The bladder must not be allowed to call out to the child but the child taught to call out to his bladder. Mothers will say that they cannot do this while the child is at school, but if they start on Saturday morning and keep the child at home from the cinema, it is a fact that the majority have got up to an hour by Monday. We cannot expect night control until day frequency has been reduced to at least two hours.

### CONCLUSION

To sum up from the point of view of a surgeon presented with this problem of enuresis in the child, the following facts emerge:—

First, a universal and simple classification according to their symptoms.

Secondly, we may say that no urological or neurological examination is complete without cystometry. This special examination can be carried out very simply and may yield information of value, although in the majority of cases it will merely confirm the bladder age.

Thirdly I believe that greater attention should be paid by physicians and surgeons to minor cerebral damage and that it may be due to anoxia under anæsthetic or following whooping cough or head injury. I need not dwell upon the fact that quite a lot of surgical operations, mainly local authority raids on the naso-pharynx and dental extractions, are performed with asphyxia as the main form of anæsthetic and we should do all in our power to support our colleagues in the Faculty of Anæsthetists in their effort to introduce their great art even into the recesses of Casualty Departments and School Clinics.

Fourthly, we must take cheer from the fact that over 90 per cent. of cases seen can be improved materially in a matter of a few weeks.

Fifthly, the history never comes out at the first session and even the surgeon should see the case more than once. He should acquaint himself with pædiatric knowledge and equip himself with instruments of appropriate size. For the surgeon to send the case for psychotherapy, merely because his instruments are too big or his patience too small, is as irresponsible as it is fruitless. I have seen little evidence that psychiatry can improve this urinary disability although it may remove a lot of overlay. The parents require help themselves and very often to be told that the child is nervous or is mentally disturbed does *not* help.

If I were an artist I would draw three horses. It is difficult in many cases to say whether uropathology has followed the incontinence or has caused it. It is not so difficult to realise that lifelong incontinence with its ammoniacal and fishy environment night and day drags in its train a distorted mental outlook to say the least. I would, therefore, harness my three horses and depict them drawing a cart. In the cart I would put the dreams, the phobias and obsessions, the passions, the disorders of behaviour and even the psychiatrist, by whose efforts this team may need to be kept on the road to social adaptation.

Enuresis is a developmental error in 70 per cent. of the cases. The others are due to physiological reversion which I believe may in turn be due to cortical damage and is very seldom psychogenic. There are skeletons in the cupboards of most children's minds but they are not necessarily enuretic skeletons. I believe one great hope lies in educational psychology.

I would like to acknowledge with gratitude the encouragement I have received from Mr. Twistington Higgins and the unceasing help of the medical, nursing and lay staff of St. Bartholomew's, The Hospital for Sick Children, Great Ormond Street, and the Children's Hospital, Sydenham.

The problem confronts physicians, surgeons, anæsthetists, physiologists, educationists and administrators.

To quote again, "The incontinent child should be examined by a doctor." Perhaps, one day, we will be able to revert to the spelling of the physicians EN-EURESIS and say with Hunter, in the memory of whose name this lecture was given, ἐν-εὐρηκα θιτιαν.

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## SAYINGS OF THE GREAT

“The Master said—Learning without thought is useless ; thought without learning is perilous.”—*Analects of Confucius*. (Submitted by J. R. Rose, F.R.C.S.)

“Nor bring, to see me cease to live,  
Some doctor full of phrase and fame,  
To shake his sapient head and give  
The ill he cannot cure a name.”

*Matthew Arnold.*

(Submitted by W. Anderson, M.B., Ch.B., F.R.C.S.)

“We are accustomed to see men deride what they do not understand.”  
*Goethe*. (Submitted by C. Allan Birch, M.D., F.R.C.P.)

“The secret of the care of the patient is in caring for the patient.”—*Francis Peabody*. (Submitted by C. Allan Birch, M.D., F.R.C.P.)

“To perform an operation is to mutilate a patient we cannot cure ; it should therefore be considered as an acknowledgement of an imperfection of our art.”  
—*John Hunter*. (Submitted by C. Allan Birch, M.D., F.R.C.P.)

“Hunter saw, as from a peak in Darien, the illimitable ocean of biology before him and he addressed himself unhesitatingly to explore it all.”—*Wilfred Trotter*. (Submitted by Ronald W. Raven, O.B.E., F.R.C.S.)

## “OBSERVABLES” AT THE ROYAL COLLEGE OF SURGEONS

### 23. THE FELLOWSHIP SIGNATURE BOOK

THE GREAT MAJORITY, if not all, of the Fellows of the College will remember the large book, commonly known as the Fellowship Signature Book which was one of the documents they were required to sign giving their “full Christian names and a permanent home address,” after being congratulated by the Court of Examiners on their success in the Final Fellowship Examination. Few, however, will have realised that the same book was in use for this purpose for over 100 years from 5th December, 1844 to 27th February, 1948.

This is the book of the Bye-Laws and at all times contains the Bye-Laws of the day corresponding with those contained in the pink-covered booklet issued to the successful candidates. The Bye-Laws inscribed in the front of the book in 1844 were in consonance with the 1843 Charter which gave the College power to institute the Fellowship, and amendments have been added to the book at intervals on the eight subsequent dates when the Bye-Laws have been altered.

The first signature in the book is that of ROBERT MARTIN, of Holbrook, near Ipswich, the first man to pass the Final Fellowship Examination, though not actually the first Fellow; for over 500 senior Members were elected without examination to the Fellowship within a year of the granting of the 1843 Charter.

Each of the first two pages contains the signature of a future President, LUTHER HOLDEN on the first, and JOHN ERIC ERICHSEN on the second (Fig. 1).

To look through the pages of this book is to be confronted by well-known names at every turn and to marvel that some of the signatures had or have changed so much and others so little with the passage of years.

The signature of JOSEPH LISTER of Upton, Essex, appears on a short page of six names for 8th December, 1852, and incidentally the changing face of London is indicated by the fact that two of these six signatories gave as their address Kennington and New Kent Road respectively.

There is a page of 17 signatures in 1906, no less than six of whose owners reached the Council or Court of Examiners, or both.

The book was about three-fifths spent when there first appeared the signature of a lady, ELEANOR DAVIES-COLLEY, of 16, Harley Street, W., on 1st December, 1911.

A new Signature Book came into use with the Bye-Laws granted in May, 1948, and the last entry in the old book was the signature of DOUGLAS BURLAND DUFFY, of 406, Glenferrie Road, Hawthorn, E.2, Victoria, Australia (27th February, 1948):

K.C:

Subscriptions to the Bygone and Yellow notices of the R.C.S.		Observations		Date		Name		Residence	
1	1845-46	1	White - M. L. M.	16	1845	1	Henry King	1	13 St. Anne's
2		2	White - M. L. M.	17	1845	2	James B. B. B.	2	13 St. Anne's
3		3	White - M. L. M.	18	1845	3	George B. B. B.	3	13 St. Anne's
4		4	White - M. L. M.	19	1845	4	George B. B. B.	4	13 St. Anne's
5		5	White - M. L. M.	20	1845	5	George B. B. B.	5	13 St. Anne's
6		6	White - M. L. M.	21	1845	6	George B. B. B.	6	13 St. Anne's
7		7	White - M. L. M.	22	1845	7	George B. B. B.	7	13 St. Anne's
8		8	White - M. L. M.	23	1845	8	George B. B. B.	8	13 St. Anne's
9		9	White - M. L. M.	24	1845	9	George B. B. B.	9	13 St. Anne's
10		10	White - M. L. M.	25	1845	10	George B. B. B.	10	13 St. Anne's
11		11	White - M. L. M.	26	1845	11	George B. B. B.	11	13 St. Anne's
12		12	White - M. L. M.	27	1845	12	George B. B. B.	12	13 St. Anne's
13		13	White - M. L. M.	28	1845	13	George B. B. B.	13	13 St. Anne's
14		14	White - M. L. M.	29	1845	14	George B. B. B.	14	13 St. Anne's
15		15	White - M. L. M.	30	1845	15	George B. B. B.	15	13 St. Anne's
16		16	White - M. L. M.	31	1845	16	George B. B. B.	16	13 St. Anne's
17		17	White - M. L. M.	32	1845	17	George B. B. B.	17	13 St. Anne's
18		18	White - M. L. M.	33	1845	18	George B. B. B.	18	13 St. Anne's
19		19	White - M. L. M.	34	1845	19	George B. B. B.	19	13 St. Anne's
20		20	White - M. L. M.	35	1845	20	George B. B. B.	20	13 St. Anne's
21		21	White - M. L. M.	36	1845	21	George B. B. B.	21	13 St. Anne's
22		22	White - M. L. M.	37	1845	22	George B. B. B.	22	13 St. Anne's
23		23	White - M. L. M.	38	1845	23	George B. B. B.	23	13 St. Anne's

Fig. 1. The first two pages of The Fellowship Signature Book



MY LORD,

I did myself the honor to wait upon your Lordship, to thank you for your very polite and obliging Letter. Conceiving it possible, that your Lordship might not be acquainted with the inferior parts of the Treasury and to save your Lordship the trouble of inquiring the mode ; I wrote to a friend of mine belonging to the customhouse, and he sent me in answer the enclosed which I take the liberty to enclose to your Lordship. The man's name is John Taylor aged 45 your Lordship will I hope excuse this trouble, as it is intended to lessen another. I hope this Country will once more rise in fame. I think it has still some powers left, and I am certain your Lordship has resolution to use them. Long may you live to save it is the wish of your Lordship much obliged and most Humble servant.

JOHN HUNTER.

Augst 16, 1782.

While looking up the names cited in these letters I came upon an account of the Marquis of Rockingham's\* last illness, death and post-mortem examination, recorded by Hunter himself. The descriptions, apparently unpublished, may suitably find place here to balance the lack of medical material in the letters. The account of the illness is as follows :—

### HUNTER'S MANUSCRIPT CASE-BOOK (p. 708)

#### HYDROPS PECTORIS (*crossed through*)

#### The Marquis of Rockingham's Case

About the Year One thousand seven Hundred and fifty Nine, he said that he had a fall from his Horse ; in this fall he said he was thrown several Yards, and received a hurt about the Pitt of the Stomach. How far he was sensible at the time to know he had received a blow there, I am not certain, but from that time to his death, he complained of pain in that part.

The account given of this supposed fall by a Gentleman that was present is the following, that the Marquis did not fall, but by pulling up the Horse forcibly and quickly to keep him from stumbling, that he conceived he had torn some of the fibers of the part. The pain was such as generally arises from the Par Vagum and Intercostal Nerves when diseased Viz Oppressive ; and appeared to be either the cause of, or was greatly increased by Wind in the Stomach and Intestines, for Wind was observed to be often moving in the bowels at those

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\* *Charles Watson-Wentworth, 2nd Marquis of Rockingham* (1730-July, 1782), the subject of the above notes, was educated at Westminster School and St. John's College, Cambridge. He was elected F.R.S. in 1751 and was installed K.G. on the 6th May, 1760, and on the accession of George III, continued in the office of Lord of the Bed-chamber which he had held since 1751.

He was assiduous in attendance on Keppel during his court-martial at Portsmouth, and, on the Admiral's acquittal, moved in the House of Lords a vote of thanks for his outstanding services. He also delivered an address on the impoverished state of Ireland and led the attack on Lord Sandwich's administration of the Navy which sent Kampenfeldt to sea with an inadequate force.

He was a Whig of sterling honesty who fought strenuously against a corrupt system of government. Although twice Prime Minister, the King had no great opinion of him but he misjudged the Marquis ; a far better estimate of Rockingham's worth was that of Burke who esteemed him as a man of sound principles, enlarged mind, clear and sagacious sense, and unbroken fortitude.

times, and when it passed it gave ease. The pain was not constant ; but I do not know if any reason could be assigned for its returns. Every Physician and Surgeon in Europ of any Note was consulted, and various were the opinions of the cause of this Pain. It was sometimes imagined that a hardness was felt externally in the part, but that idea again vanished. The Liver, Gall bladder and ducts were very much suspected. Blisters, Caustics, Plaisters etc were applied to the Part, and all the Warm and Nervous Medicines were prescribed, as also Opium to quiet. He probably visited every Bath in Europ as also every kind at Bath but nothing appeared to give any relief. The two last Years of his Life he took too violent Exercise, as hunting as also setting late up at Night, but all this was with a view to divert the mind for it was anxiously interwoven with the affairs of the Nation, and for the last ten Years of his Life he was the support of an Opposition to the pursuit of those Measures which he had (when in power) given up ; and for the last half Year of his Life was (probably) planning the best mode of doing again the same thing.

These circumstances most probably created or encreased his anxiety of Mind, which always encreased, or even seemed to renew the Pain.

His own idea of the disease was, that there was some unnatural Substance formed or lodged in the part ; sometimes it was a Solid, often a fluid as Water, and at other times it appeared to be air. He conceived that by opening the belly the disease might be discover'd, and relief of course might be procured, and when in much pain ; he would often solicit an operation but none chose to perform an Operation without a visible diseased guide.

For some Weeks before death he was not quite so well as usual in other respects at times a little short breath'd, and for some days before death he made but little Water ; but the Old complaint did not abate upon the commencement of others, but rather encreased, and on the Morning of his death the pain and oppression became so violent that he became almost outrageous for some operation to be attempted, and said that if something was not immediately done to relieve him he could not possibly live many hours. a few hours before Death he had the following Symptoms. The pain at times was excessive, and then he seemed to be roused into a sensibility of Mind for then he was clear in his imagination, and seemed to have considerable Strength of body, but he would immediately fall into a kind of Stuper with his Eyes half shut, and in this Stuper he did not breath, this cessation of breathing each time lasted about twenty seconds and when he came out of this, or was spoke to, he then breathed much stronger than common, as if making up the lost time. The pulse was weak but regular and did not appear to be much affected by the peculiar mode of breathing. He all along, could lie down perfectly horrizontally, either on his back or on either side equally.

His bowels were regular.

Just before death one of these cessations of breathing became longer than usual, the constitution appeared to be sensible of it for he was thrown into convulsions the face became black as if choking and he seemed to give two or three strong inspirations and expired.

*Vide Dissections No. 191.*

The Case-book was written up by an amanuensis with corrections and additions by Hunter himself. At the end of the above account a separate slip, entirely in his handwriting, is inserted and runs :

As this case had call'd forth the attention of almost every Physical man in London and nothing had ever been made out ; the appearance after death became an object of inquiry, and many were anxious to be present at the examination which was attended by Dr. Wm. Hunter, Dr. Warren, Mr. Bromfield and opened by J. Hunter.

The post-mortem findings are recorded in

*Morbid Appearances in Dead Bodies.* Manuscript, P.317

**No. 191. The appearances upon opening the Body of the Marquis of Rockingham**

As the seat of the disease appeared to be about the Pitt of the Stomach great attention was paid to this part in the Mode of opening, and instead of an incision made down the *Linea alba* a crucial incision was made from the margin of the Thorax laterally across the Navle to each [crest] of the Ilium ; this preserved regarding the Pitt of the Stomach intire ; and upon raising the flap and looking under it, we found no adhesion and every thing to appearance in a Sound State. The Sternum was next removed, and in the seperation of the diaphragm from the Sternum etc its attachment was carefully examined but nothing preternatural could be observed. upon examining every Viscus in the Abdomen, every thing was found perfectly Sound as to Structure both the external and internal appearance and also when cut into. In the Cavity of the Thorax we found a considerable quantity of Water. in the right side there was a quart and the best part of a pint ; and in the left above a pint and a half. The water was a pretty clear Serum.

The Lungs were perfectly sound, not the least adhesions anywhere.

The Heart was large and strong in its coats and full of coagulated Blood. Two of the Semelunar Valves were ossify'd in some parts but not remarkably so.

From the foregoing it is clear that Hunter was present at Rockingham's last illness, the concluding phases of which he observed with characteristic keenness. The post-mortem failed to account for symptoms of more than 20 years' duration but Hunter entered the case as one of "Hydrops pectoris" in his Case-book. Such an affliction might well have caused Rockingham to seek relief at "every Bath in Europ as also every kind at Bath."

S. WOOD

Assistant in the College Library.

## MONTHLY DINNERS

Monthly dinners are held in the College on the Wednesday before the second Thursday of each month. The following are entitled to attend with their guests: All Diplomates and students of the College and Members of the Associations linked to the College through the Joint Secretariat. It is not necessarily intended that guests should be members of the medical profession.

The dinners will be at 7 p.m. on the following Wednesdays: December 7, 1949, January 11, February 8, March 8, April 12, May 10, and June 7, 1950. There is an inclusive charge of £1 5s. (including drinks), which must be sent with the application to the Assistant Secretary at least a week before the date of the dinner. The dress is Lounge Suit or Uniform.

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### DIARY FOR NOVEMBER (16th-30th)

Wed. 16		D.T.M. and H. Examination begins.
	5.00	PROF. T. CRAWFORD—General Pathology of the Central Nervous System.
Thur. 17	3.45	MR. R. J. LAST—Arnott Demonstration.*
Fri. 18		D.A. Examination (Part II) begins.
		Board of Faculty of Dental Surgery.
Mon. 21	3.45	DR. W. FELDBERG—Pharmacology.
	5.00	PROF. T. CRAWFORD—General Pathology of the Central Nervous System.
Tues. 22	3.45	DR. JAMES CRAIGIE—Imperial Cancer Research Fund Lecture—A Quantitative Approach to the Study of Transplantable Tumours.*
	5.00	DR. W. FELDBERG—Pharmacology.
Wed. 23	3.45	PROF. D. V. DAVIES—Basis Cranii Externa.
	5.00	PROF. T. CRAWFORD—General Pathology of the Central Nervous System.
Thur. 24	3.45	PROF. D. V. DAVIES—Basis Cranii Interna.
	5.00	SIR HENRY WADE—Thomas Vicary Lecture—The Barber Surgeons of Edinburgh.*
Mon. 28	3.45	PROF. D. V. DAVIES—The Orbit and its Contents.
	5.00	PROF. T. CRAWFORD—General Pathology of the Central Nervous System.
Tues. 29	3.45	DR. C. H. ANDREWES—Imperial Cancer Research Fund Lecture—The Virus Theory of Cancer in the Light of Recent Work.*
Wed. 30		Second L.D.S. Examination begins.
	3.45	PROF. D. V. DAVIES—The Paranasal Sinuses.
	5.00	DR. N. H. MARTIN—The Application of Biochemistry to Clinical Problems.

\* Not part of courses.

## DIARY FOR DECEMBER

Thur.	1		D.P.M. Examination (Part I) begins.
	5.00		PROF. GEOFFREY JEFFERSON—Otolaryngology Lecture—Intracranial Abscess.*
Fri.	2		First L.D.S. Examination and D.P.H. Examination (Part I) begin.
	3.45		PROF. D. V. DAVIES—The Veins and Lymphatics of the Scalp and Face.
	5.00		DR. N. H. MARTIN—The Application of Biochemistry to Clinical Problems.
Mon.	5	3.45	PROF. D. V. DAVIES—The Salivary Glands.
	5.00		DR. BERNARD JOHNSON—Anæsthetics.
Tues.	6	3.45	DR. A. HUXLEY—Central Nervous System.
	5.00		DR. BERNARD JOHNSON—Anæsthetics.
Wed.	7	3.45	PROF. J. D. BOYD—Development of the Heart and Cardiovascular System.
	5.00		DR. N. H. MARTIN—The Application of Biochemistry to Clinical Problems.
Thur.	8	5.00	Board of Faculty of Anæsthetists.
			First Membership Examination and D.P.M. Examination (Part II) begin.
Fri.	9	5.00	MR. R. J. LAST—Arnott Demonstration.*
	3.45		D.I.H. Examination (Part II) and D.L.O. Examination (Part I) begin.
	5.00		MR. E. C. B. BUTLER—Applied Anatomy of the Colon.
			DR. N. H. MARTIN—The Application of Biochemistry to Clinical Problems.
Mon.	12	3.45	MR. E. C. B. BUTLER—Applied Anatomy of the Rectum and Anal Canal.
	5.00		DR. N. H. MARTIN—The Application of Biochemistry to Clinical Problems.
Tues.	13	3.45	PROF. J. D. BOYD—Development of the Genito-urinary System.
	5.00		DR. N. H. MARTIN—The Application of Biochemistry to Clinical Problems.
Wed.	14	3.45	PROF. J. D. BOYD—Development of the Nervous System.
	5.00		DR. H. F. BREWER—Hæmatology.
Thur.	15		Pre-Medical Examination begins.
	3.45		PROF. J. BEATTIE—Peripheral Autonomic System.
	5.00		DR. A. HUXLEY—Central Nervous System.
Fri.	16		D.L.O. Examination (Part II) begins.
Mon.	19	3.45	PROF. J. BEATTIE—Peripheral Autonomic System.
	5.00		DR. H. F. BREWER—Hæmatology.
Tues.	20	5.00	MR. R. J. LAST—Arnott Demonstration.*
Wed.	21	3.45	PROF. J. D. BOYD—Development of the Pharyngeal Derivatives and Endocrine Glands.
	5.00		DR. A. HUXLEY—Central Nervous System.
Thur.	29	3.45	PROF. T. NICOL—Applied Anatomy of the Thorax.
	5.00		DR. A. HUXLEY—Central Nervous System.
Fri.	30		D.P.H. Examination (Preliminary) begins.
	3.45		PROF. T. NICOL—Applied Anatomy of the Kidneys, Ureter and Bladder.
	5.00		DR. H. D. ROSS—(Subject to be announced).

\* Not part of courses.

# THE BARBER SURGEONS OF EDINBURGH

Thomas Vicary Lecture delivered at the Royal College of Surgeons of England  
on  
24th November, 1949  
by  
Sir Henry Wade, C.M.G., D.S.O., F.R.C.S.E.

MR. PRESIDENT, Master of the Worshipful Company of Barbers, Ladies and Gentlemen :

For the second occasion within recent years I desire to thank the President and Fellows of the Royal College of Surgeons of England for the great honour they have conferred on me in appointing me Thomas Vicary Lecturer for this year.

The occasion awakens vivid memories of an evening when I had the privilege, through the influence of Lord Webb-Johnson, of dining with the Worshipful Company of Barbers, examining their treasures and being looked down upon by His Gracious Majesty, King Henry the Eighth and his faithful servant Thomas Vicary. As they gazed down upon me enjoying a life-long desire, I was supremely happy.

To-night I feel I may be permitted to tell you of my conversation with Thomas Vicary, newly elected Master of the United Company of Barbers and Surgeons. We spoke of the Barber Surgeons of Edinburgh and much that had happened since he retired from practice.

I mentioned how deep was our gratitude to King Henry's sister, Margaret Tudor, and her husband, King James the Fourth of Scotland for a dual service done. Firstly, they founded the British Empire by being responsible in their offspring for the union of the Crowns of England and Scotland. A happy event which owned its origin to a few young Scottish Border yokels who

"went over to the town of Norham which was near the Castle (as they used to do frequently in Times of Peace) there to recreate themselves in sports and pastimes and to junket together with their neighbours. The Garrison in the castle, out of the Rancour yet lodging in their breasts since the former war and being also provoked by some passionate words, accused the Scots of being spies, and so from words came to blows, and the Scots returned home with the loss of some of their company."

James was very angry and threatened to declare war. Bishop Fox of Durham who owned the castle, pacified him and through his good offices the King became engaged to Margaret Tudor, daughter of Henry the Seventh. Ultimately, their great-grandson, James the Sixth became James the First of England.

Secondly, the Scottish Surgeons were grateful to King James the Fourth for awarding the charter of privileges of the Barber Surgeons, and for the keen personal interest he had in the practice of Surgery.

## JAMES THE FOURTH—The Man and his time

What sort of man was this King? He was a Stuart, a race of Kings uniformly beloved of their people and murdered by their nobility. One who "to give a testimony to the world of the Agonie of his mind, for the Death of his Father, and what remorse and anguish he suffered for the faults of those who brought him to the Field against him, he girded himself with a chayn of Iron, to which every third year of his life thereafter he added some rings and weight."

His great-grandfather, James the First, the beloved statesman, jurist, linguist, author and poet, was murdered in the Blackfriar in Perth. A maid of honour of the name of Douglas tried to save his life, and finding the traitors had removed the bar from the chamber door, thrust her arm in the place where it should have passed, but (says the ancient chronicle) that easily broken, the conspirators rushed into the chamber and murdered their King. Thus died at the age of 44 after reigning 13 years, he who set as his royal decree :

"The Key shall keep the Castle and the bracken bush the Cow."

He was succeeded by his son, aged six years, who had the title of James the Second, and who was kidnapped and kept a prisoner by the unpopular nobility, who had usurped power. They were outwitted by his mother, who came from Stirling and returned there with the young King, her son, in a linen trunk.

He, in his turn, lost his life later when a cannon burst during the siege of Roxburgh Castle and was succeeded by his young son, aged seven, who was crowned at Kelso, as James the Third. The father, who had a broad red spot on one of his cheeks, from which he was named by his countrymen "James with the fiery face," is described as "upright, sincere, affable, courteous, loving to his domestics, humane toward his enemies, gracious and benign to all men, and a lover of justice."

Of James the Third it may be said he was not made of the sterner stuff required to control a nobility whose pastime was theft (called raiding) and whose final political argument was murder. His mother, knowing her boy, spoke to him on her death bed, and told him, "make yourself beloved and feared both together, since love alone of itself is often the cause of contempt, and fear alone begets hatred. Remember ye govern not the soft effeminate people of the South, but a fierce warlike nation of the North, which oftener use to be entreated than commanded by their Princes."

When he had grown to manhood's estate, the rebels, who on this occasion came from South of the Highland Line, claiming as their excuse that he had surrounded himself with men of no account to the contempt of the nobility, mobilised, and, having corrupted his keepers and threatened to give up the kingdom to the King of the English, persuaded the young Prince of Rothesay, a lad of 15, to go with them, to give lustre

to their actions, shadow their rebellion and be the titular and painted head of their arms.

The North rallied to the King and the forces met at Sauchie Burn, near Bannockburn. The King's army was defeated and in the rout of horse and foot, the King, seeking to retire, was thrown from his horse on leaping a ditch, and being sore bruised, he was carried to a mill at Bannockburn where some reported that one masquerading as a priest, after shriving him, stabbed him with his dagger and killed him in cold blood, despite the express and strict command by his son, the Prince of Rothesay, that none should pursue his father. Thus at the age of 35, in the 29th year of his reign, he died.

### **The King's Girdle of Repentance**

"The rebels, to make their Rebellion lawful and show the world they intended not the subversion of their Country, but of their opinionative King, nor that they did dislike Sovereignty, so they might have a prince who would be ruled by their directions, take the name, and leave to them the Majesty and Authority of his Place, after the killing of the Father call a Parliament for the installing of the Son in the Royal Throne."

Hence came the iron girdle.

His mother, the daughter of the King of Denmark, brought with her as her dowry as a gift to the nation, the islands of Shetland and Orkney, and probably from her Viking blood he inherited his love of exploration and adventure.

### **The King and his Navy**

It is not surprising that the call of the blood turned his thought to the seas, and Scotland, for the one and only time, became a great naval power. He created a Scottish Fleet of 24 ships, the largest of which, the dreadnought of its day, the Great Michael, was launched at Newhaven, Edinburgh's foreshore in 1511.

### **The King as an experimental Chemist and Alchemist**

Under the direction of, and in cooperation with, an Italian, John Damian, he set up furnaces and laboratories at Stirling and Linlithgow, where at considerable expense to himself and the State, research work was carried out to discover an elixir of life and a means of transforming baser metals into gold.

### **The King's interest in Aviation**

John Damian, who had been promoted Abbot of Tunland, now metaphorically and actually spread his wings further. He intimated that on a certain day he would fly through the air from the rock of Stirling Castle and land in France, and duly on the appointed day, before an immense crowd, wings were coupled to both his shoulders and he set forth from the rock. Unfortunately he had barely begun when he fell



Altar within the College Kirk of St. Giles in the honour of God and St. Mungo, their patron, and that they had maintained the same by their humble weekly penny which, although small in amount, sustained and upheld the said Altar in all necessary things." They claimed to have been good citizens, "taking their share in walking, warding, stenting and bearing of their charges within the Burgh at all times." They requested that they might yearly choose amongst themselves a Kirk Master and Ourisman," whom the whole brethren of the craft should obey for that year; that no manner of person occupy or use the practices of the said Craft of Surgeon or Barber within the Burgh unless he first be a Freeman and Burgess of the City and that he be worthy and expert in all the practices belonging to the said Craft, be diligently and carefully examined and admitted by the Masters of the said Craft and that every man that is to be made a Freeman and Master to be examined and proved in the following subjects, that he know anatomy, the nature and complexion of every member of the human body, and likewise he know all the veins of the same that he may make phlebotomy in due time, and also that he know in which member the sign has domination for the time for every man ought to know the nature and substance of everything he works or else he is negligent; that once a year they obtain as the subject for anatomical dissection the body of a condemned man after he be dead to make anatomy on 'quhairthraw we may half experience ilk ane to instrict vtheris, and we sall do suffrage for the soule, and that na barbour, maister nor seruand, within this burgh hannt (practice) vse nor exerce the craft of Surregenrie without he be expert and knaw perfytelie the thingis abouewritten,' and whatever person happens to be admitted Freeman or Master to the said Craft or occupies any position of the same, shall pay at his entry five pounds Scots to the reparation and upholding of the said Altar of St. Mungo for divine service to be done thereat, with a dinner to the Master of the said Crafts at his admission and entry, excepting that every Freeman Master of the said Craft and his lawful sons to be free of any money payment except the dinner to be made to the Masters of the said Craft after he be examined and admitted by them: that no Master of the said Craft shall take an apprentice for admission to the Surgeon Craft without he can both write and read and the apprentice shall pay on his entry the sum of 20s. to the said Altar, that every Master that is a Freeman of the said Craft shall pay a weekly penny and every servant shall pay a weekly half-penny to the said Altar: that they shall have power to chose a chaplain to do divine service. Lastly, no person, man or woman, within this Burgh shall make or sell any aquavite (whisky) within the same, except the said Maisters, Brethren and Freemen of the said Crafts under the pain of confiscation of the same with consideration."

The Petition was duly agreed to, and for the greater verification and strength of the same, the Common Seal of Cause at Edinburgh on the first day of the month of July, the year of God, One Thousand, Five Hundred and Five, was affixed.

The Surgeons and Barbers Award was the Tenth Seal of Cause, granted to various Crafts.

They were as follows :—

1474	February 18th	The Hatmakers.
1474	December 2nd	The Skinners.
1475	October 15th	The Wrights and Masons who previously on that day had been granted the Aisle and Chapel of St. John the Baptist.
1476	January 31st	The Wobsters.
1483	May 3rd	The Hammermen.
1488	April 11th	The Fleshers.
1489	August 26th	The Coopers.
1500	August 20th	The Walkers.
1500	August 26th	The Tailors.
1505	July 1st	The Surgeons and Barbers.

A common policy runs through all.

The claim by statement or inference of inefficient services on the part of certain craftsmen.

The desire to establish a corporation to train apprentices, and to discipline their members.

To have the power of electing officials, a Deacon or Kirkmaister, and a small Council to be responsible for the education, registration and the discipline; to inspect the standard of the work of their craftsmen, to receive complaints of unsatisfactory work and to take action accordingly. The customary procedure was the imposition of a fine for the first and second offences. On the third occasion the culprit was handed over to the Lord Provost and Magistrates to be dealt with.

It was obligatory for each craft to support a Chapel to their Saint in the Collegiate Kirk of St. Giles and all fines imposed, whether in cash or in kind, were awarded to the Chapel for its maintenance.

Although a monopoly was asked for and granted, an outlander coming to the City to practise his craft could be admitted after examination by the Council. In every case the absconding or suborned apprentice was punished. When the apprentice was the son of one of the members, he was awarded special concessions—reduced fees or a shorter apprenticeship.

*The Hatmakers* favoured an apprenticeship of five years, to be three in the case of members of the craft. The practical examination consisted of making two pieces of work; in the case of sons of craftsmen, one piece.

They thought it right, speedful and profitable that none of the craftsmen of hat-making should sew, renew or mend “any auld hattis.”

*The Skinners'* petition set a standard. Previous to their application they had founded an Altar to St. Christopher in the Kirk of St. Giles and obtained authority to levy toll on their members for its maintenance and, on receiving an apprentice, to pay five shillings. In their petition they claimed that many of their craftsmen were remiss and they obtained authority to make a collection every Monday and those who did not pay to the collection could be put in the stocks. Members who failed, without due cause, to attend meetings of the craft when summoned, had to pay half a pound of wax to St. Christopher's Altar.

For faulty description of any article, such as a girdle described as of doeskin when made of sheepskin, or selling an article of bad workmanship, after trial by the Deacon and small Council they were liable to a fine of half a pound of wax to the Altar of St. Christopher for the first offence; one pound for the second, and for the third offence to be brought before the Lord Provost and Baillies.

*The Wrights and Masons* shared the Aisle and Chapel of St. John the Baptist which had been granted to them on the morning of their application for a Seal of Cause. They desired to have authority to supervise the work done by their craftsmen, and their efficiency, by appointing four men, the best and worthiest of the two crafts, two masons and two wrights, as inspectors "who shall visit and examine all work of the craftsmen and see that it is honestly and truly done; any complaints to be similarly dealt with and if indicated to give instructions for the wrong to be amended and if not carried out, the Provost and Baillies to order the repair to be carried out; the apprenticeship to be for seven years with entrance fee of half a merk to the Altar; the penalty of an absconding apprentice to be one pound of wax, for the second offence, two pounds, for the third, remission to the Provost."

They concluded with a homely request which to me, as one who recently walked down the Royal Mile in procession, has an especial appeal: "That the two craftsmen already mentioned shall arrange to have their place and precedence in all general processions such as they have in the town of Bruges or such like good towns."

*The Wobsters*, in their application, request "to be granted certain statutes for supplying and upholding of divine service founded and upheld by them to St. Seueraine in St. Giles Kirk. No man to be a Master unless he be made a Freeman. Subsequently, he is to be examined by the Deacon and four men of the craft and his tools inspected. If he passes, the fee to be two pounds of wax to the Altar, but if he be a Burgess's son, half a merk to the Altar."

In the *Hammermens'* petition they propose that "every Saturday afternoon two or three of the worthiest Masters with knowledge of the said

craft to have power to go with an officer to examine the men of the said craft's work, if it be sufficient in stuff and workmanship, good worthy and creditable to serve the King's lieges with and if it be found faulty, to forbid the same to be sold under the penalty of forfeiture."

In the *Fleshers'* Seal of Cause they petitioned that "any of their craftsmen who buy and sell infected meat or fish, he be deprived of his freedom, the goods confiscated, and given to the sick folk in the Almous, and he to be banished from the town."

In Jamieson's Dictionary of the Scottish Language, the note on Almous is as follows:—"So late as the reign of James IV licenses were granted by the several universities to some poor students to go through the country begging, in the same manner as the poor scholars belonging to the Church of Rome do to this day in Ireland. Among those designated 'ydill and strang beggaris,' are reckoned—'all vagaboundis scollaris of the vniuersiteis of Sanetandrois, Glasgow and Abirdene, not licencit be the rector and dene of facultie of the vniuersitie to ask almous.'"

They also petitioned "to engage apprentices who must first become a Freeman of the town and if he qualifies he pay his due to the Craft and Altar."

*The Coopers'* petition mentions that many of their craftsmen had been most remiss in paying their weekly penny to the Wright's Altar to St. John to which they were affiliated; the agreement to be that each apprentice pay five shillings on entry.

The decision was that all privileges granted to the Wrights be conferred on the Coopers.

*The Walkers or Shrinkers of Cloth* state in their petition that the Altar of St. Mark, Philip and Jacob in St. Giles was established and maintained by them and "for its support every Freeman when he sets up in business, to pay five crowns to the Altar after he has been examined by four craftsmen, found efficient and possesses a pair of shears and has the wherewithal to pay for a supply of coloured cloth."

*The Tailors'* Altar was to St. Ann. "Apprentices to serve for seven years with special favour to the sons of said craft, entrance fee to be 10 shillings paid to the said Altar and only to be allowed to set up in business after passing an examination."

The Seal of Cause and Charter of Privileges to the *Barbers and Surgeons* agreed to by the Town Council of Edinburgh on 1st July, 1505, was confirmed by Royal Charter by King James the Fourth on October 13th, 1506, a unique distinction in that no other craft appears to have been awarded it. Probably the King's well known interest in the practice of surgery was responsible for it, and you will have noticed a number of features in their application in support of this suggestion.

Some years previously a border ploughman's coulter turned up a strange article, which we would now call a heavy bronze chemists' mortar, on which was engraved :

GILBERT PRIMROS  
CHIRURGHIE  
1569.

In the course of time it passed through various hands and ultimately was donated to Hawick Antiquarian Museum, who presented it to Lord Rosebery ; the latter, in presenting it to the College, said " I can only surmise that Gilbert Primrose, in the exercise of his volunteering proclivities or duties, must have lost his mortar on the Border in action against our old enemies the English."



Fig. 3. Mortar inscribed  
GILBERT PRIMROS  
CHIRURGHIE  
1569

unearthed by a Scottish Border Ploughman's coulter at  
the end of the 19th century.

For 143 years there was harmony ; the simple barber enjoyed the whole privileges of the craft and had frequently been treasurer and occasionally Deacon. In 1648, an act was passed that " no barber should

agree to differ as regards this steely saint in the light of the prayer he is credited with and which figures in the earliest recorded Minutes of the Barber Surgeons in 1581, a prayer which down to the present day is read at the commencement of all statutory meetings of the Royal College of Surgeons of Edinburgh; a prayer which, in these days when storm clouds again gather, I desire to repeat to you:—

“ O Eternal God, and our loving and merciful Father in Christ Jesus, seeing we are convenient heir to treat upon these things that concernis our calling, we beseik thee, O Lord, to be merciful to us, and giff us grace to proceed thereintill without malice, grudge, or partialitie; sua that the things we may do may tend to the glorie of God, the weill of our vocation, and comfort of every member of the samen; throw Jesus Christ our only Lord and Saviour. Amen.”

O Eternal God and our loving and  
 merciful father in christ Jesus pray  
 we are convenient heir to treat upon these  
 things that concernis our calling for the  
 sake of our Lord to be merciful to us  
 and giff us grace to proceed without  
 malice grudge or partialitie  
 that the things we may do may  
 tend to the glorie of God the weill of  
 our vocation and comfort of every  
 member of the samen throw Jesus  
 Christ our only Lord and Saviour Amen

John Knox

Fig. 4. The Prayer of the Royal College of Surgeons of Edinburgh, ascribed to John Knox, and recorded in the first authentic Minutes of the Meetings of the Barber Surgeons in 1581.

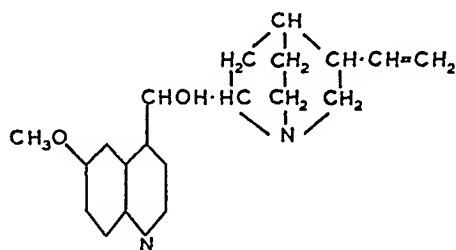
jeopardized the prospect of the control of malaria among armies deployed in endemic areas. It was fortunate that plans made early in the war on both sides of the Atlantic were already far developed with the investigation and manufacture of alternative drugs.

It had been known that mepacrine, the atebirin of Kikuth (1932) was claimed to be a useful drug for the treatment of malaria, but how its worth compared with quinine, or how toxic it would prove to be on repeated dosage, was unknown outside Germany. Great energy was thrown into the problem of investigation and research. Shannon *et al.*, (1944) investigated the distribution of mepacrine in blood and other tissues and found blood cells, especially white cells, to fix mepacrine strongly but irregularly so that plasma concentrations could not be regarded as a strict guide to blood concentrations. Nevertheless, these studies enabled a basis to be laid down for the rational use of the drug. Clinical studies in the field, with volunteers, such as those of Hamilton Fairley (1945), established the fact that the drug is essentially non-toxic, when administered in suppressive doses over long periods, and that it has some advantage over quinine.

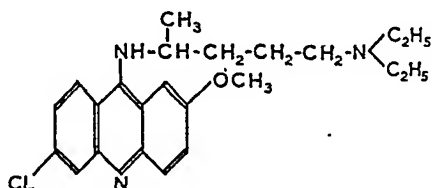
The forms of malaria encountered in service conditions were benign tertian malaria, due to *Plasmodium vivax* and malignant tertian malaria caused by *Plasmodium falciparum*. Mepacrine was found to cure malignant tertian malaria with rare relapses; on the other hand relapses were common with benign tertian.

*Malarial parasites.*—Before we can proceed with a description of the searches for more effective drugs it is necessary to consider the various forms assumed by the malaria parasite in the host. When an infected mosquito bites a man, sporozoites are transferred from the salivary gland to the circulation of the host. Until this year their immediate fate was in doubt. The work of Fairley (1945) showed that during the biting act, and for half-an-hour afterwards, blood inoculated from the bitten person produced an infection. After this period, and until the appearance of the parasites in the circulating blood, large quantities of blood from the volunteer produced no infection in another individual. The missing pre-erythrocytic stage has been discovered by Shortt, Garnham and Malamos (1948), who found schizonts in the liver of a monkey killed on the seventh day after a massive infection with *P. cynomolgi*, the causal organism of monkey malaria. The infection was by bites from infected mosquitoes and by the injection of infected mosquito tissue. The schizonts are ovoid bodies of  $26\mu$  diameter indented in appearance or with pseudopodia. The significance of this observation lies in the close resemblance between *P. cynomolgi* and *P. vivax* of human malaria, so much so as to render acceptable this observation as probably applicable to man.

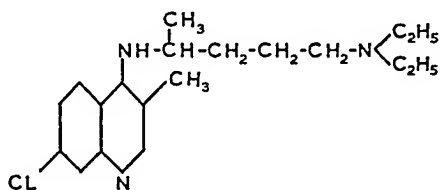
The possible explanation for the frequently observed relapses with benign tertian malaria is that the tissue-phase schizonts of *P. vivax* only are insusceptible to existing chemotherapy, or, alternatively, that the



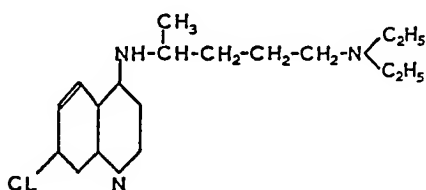
QUININE



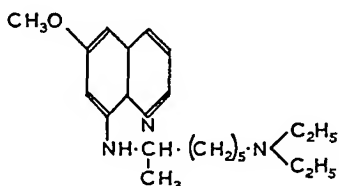
MEPACRINE (ATEBRIN)



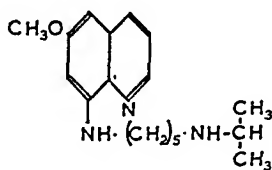
SONTOQUIN



## CHLOROQUINE



PAMAQUIN (PLASMOCHIN)



PENTAQUINE

Fig. 1. The chemical relation between the synthetic antimalarial drugs and quinine.

Early synthetic work concentrated on pyrimidine compounds. Not only were derivatives of this kind numbered among effective chemotherapeutic compounds in the bacterial field but this heterocyclic structure is an integral part of a number of essential cellular constituents, for example, nucleo-proteins. Pyrimidine derivatives might thus interfere with an essential growth factor for the malaria parasite. As the work developed no support was forthcoming to justify these views and the idea emerged that the pyrimidine ring might have no function save to provide the nitrogen atoms with the required prototrophy. This appeared to be the case and led to the synthesis of biguanide derivatives which finally pointed the way to paludrine.

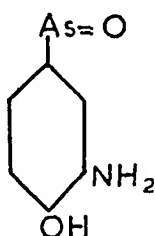
Curd, Davey and Rose (1945) found paludrine to be the only substance having a causal prophylactic action against *P. gallinaceum* in chicks,



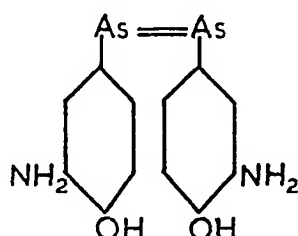
# TRIVALENT ARSENICALS



## ARSENOUS ACID



MAPHARSEN



ARSPHENAMINE

Fig. 2. In syphilis, the trivalent mapharside, or the potentially trivalent arspenamine-type represent the chemotherapeutic arsenicals.

was used instead. The result of both methods was a slight increase in the Wassermann conversion rate but also an increase of toxic effects. As a result of further experiments the duration of treatment was increased and the incidence of toxicity reduced (Eagle, 1944). The present status, as reflected by U.S. Army experience with arsenicals, is that those cases treated with arsenicals alone receive mapharside 50 mg. three times weekly for 12 weeks, or 60 mg. daily for 20 days. Each course is combined with bismuth salicylate, 0.2 gm. weekly for 12 weeks, or a total of eight doses during 20 days.

It seems proper to refer here to the value of 2:2-dimercaptopropanol in the treatment of arsenic intoxications. This substance was developed by Peters, Stoken, and Thompson (1945) as an antidote for arsenic-containing war-gases such as lewisite. This research project erected a monument to the ideal of a study of first principles which logically yielded an answer of practical application in medicine. The changes

dose for early syphilis is 4.8 million units given in 96 doses, each of 50,000 units, at two-hour intervals day and night for eight days. With depot penicillin such as oil-wax mixture (or presumably procaine-penicillin), a dose of 0.6 million units is given daily for 10 days. The second method is suitable for out-patient therapy. Treatment with mapharside and bismuth in addition did not diminish significantly the failure rate. Resistant cases may be treated with a prolonged course, combined, if possible, with fever therapy (Schwemlein *et al.*, 1948).

It is generally accepted that the immunity responses are not well developed in early syphilis and an outstanding problem left to the future to solve is whether in these cases reliance should be placed on penicillin alone. The verdict in America favours this course, while in most British clinics the current practice favours combined therapy with an additional course of arsenicals and bismuth (McElligott *et al.*, 1948).

The high efficiency of penicillin has proved a mixed blessing, since its widespread use for minor and major ailments carries with it the danger of suppressing a syphilis infection. The danger is significant when penicillin is used to treat gonorrhœa, since in these circumstances a concurrent syphilis infection may be masked. For this reason some authorities (Harkness, 1948) prefer to treat with sulphathiazole in the first instance.

#### CHEMOTHERAPY OF TRYPANOSOMIASIS

It will be recalled that the experimental chemotherapeutic studies with arsphenamine and neoarsphenamine were made in mice infected with *Trypanosoma equiperdum*. Indeed, in this sense Ehrlich prepared these and many other organic arsenicals with both syphilis and trypanosomiasis in mind. After the demonstration of the successful use of atoxyl in experimental trypanosomiasis in dogs, rabbits, guinea-pigs and rats, by Wolferstan Thomas in 1905, it was natural to try Ehrlich's compounds in Africa, where they met with considerable success in early stages of the disease before the central nervous system became invaded. Of this series the best proved to be arsenophenyl-glycin (Ehrlich, 1909). This compound had the merit of being effective against trypanosomes which had become drug-resistant to atoxyl or arsphenamine. Ehrlich found this advantage to be shared by arsenicals containing a  $\text{CH}_3\text{-CO-R}$  radicle. It is also observed in a p-arsenophenyl-butyric acid agent recently proposed (Eagle, 1945).

Tryparsamide (Jacobs and Heidelberger, 1919) proved curative in cases of cerebral involvement since it is able to penetrate the blood-brain barrier in an active form. It is, however, somewhat toxic. Neocryl, although active in early trypanosomiasis is valueless in second stage infections (Acres, 1940). This substance penetrates into spinal fluid (Hawking, Hennelly and Quastel, 1937), but is not reduced to an active molecule (Fig. 4).

The realization that while arsenicals are effective in the treatment of infections caused by *T. gambiense* they are usually much less effective in

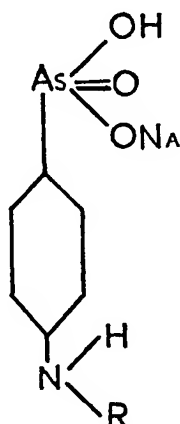

 $R = -H$ 
ATOXYL
 $R = -CH_2 \cdot CO \cdot NH_2$ 
TRYPARSAMIDE
 $R = -CO \cdot CH_2 \cdot CH_2 \cdot CO \cdot NH \cdot CH_3$ 
NEOCRYL

Fig. 4. Trypanosomiasis; the relation of the pentavalent arsenicals. Tryparsamide penetrates the blood-brain barrier in an active form; Neocryl does not.

"sleeping sickness" due to *T. rhodesiense*, led to a search for non-arsenical drugs. Ehrlich and Shiga's (1904) demonstration of the trypanocidal activity of trypan red had no practical application in domestic animals or man, but it led the way to the discovery of Bayer 205 (Germanin, suramin, antrypol) a complex urea derivative for which the German discoverers entertained high hopes (Fig. 5). It is now known to be useful only in the early stages of rhodesiense and gambiense types. It is also valuable in *T. brucei* and *T. evansi* infections. In the treatment of Surra, Mal de Caderas and other infections in animals due to *T. evansi*, suramin has been employed, with some shortcomings (Fig. 5).

More recently, King, Lourie, and Yorke (1937) investigated the potential anti-trypanosome activity of a series of guanidines isothioureas, amines, and amidines, with the result that, from a selection of aromatic diamidines, pentamidine proved of value in man (Lourie and Yorke, 1939). Pentamidine resembles suramin in proving effective in the early stages of gambiense and rhodesiense infections.

Adequate treatment of Chagas' disease, due to *T. cruzi*, is an outstanding problem. The symptoms are alleviated by Bayer 7602, Chagavlon.

Trypanosome infection of domestic animals exacts a gigantic economic toll the world over. Nowhere is the problem more grave than in Central

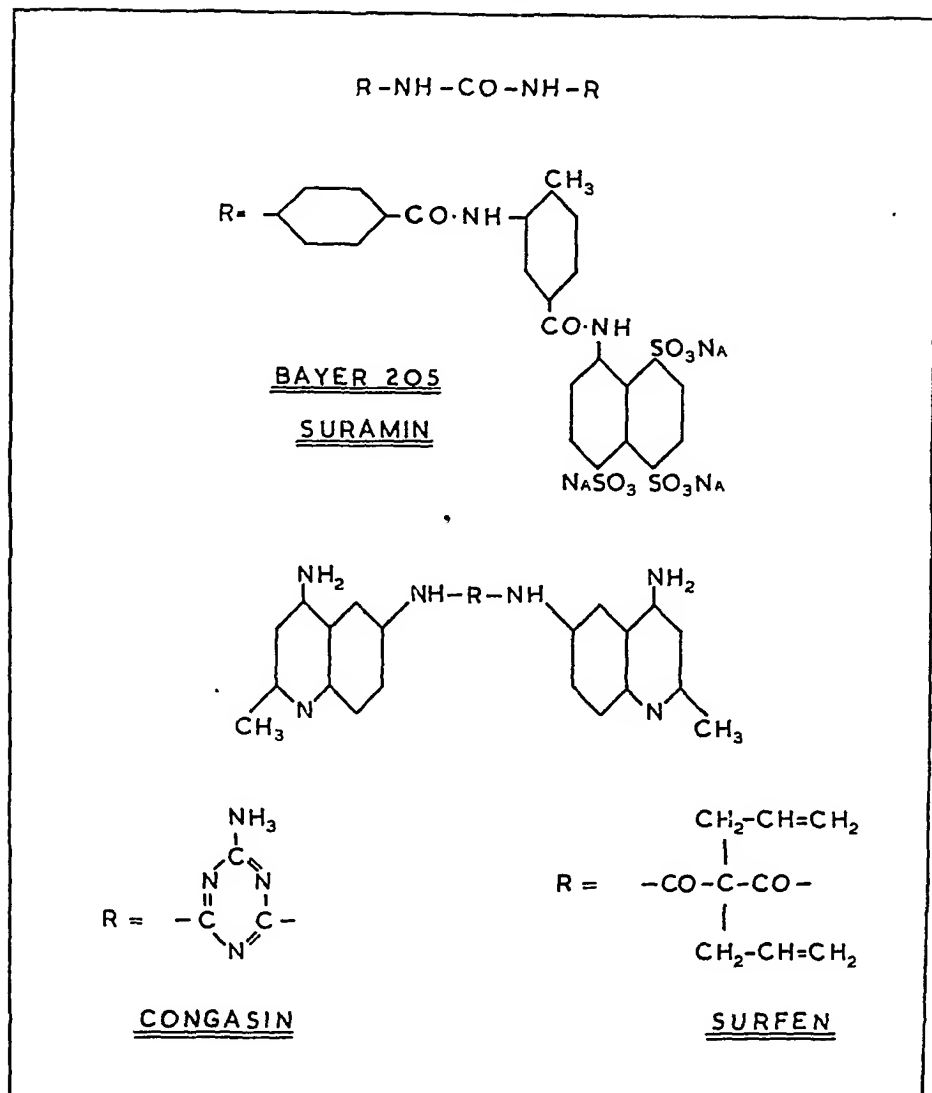


Fig. 5. Suramin, is a non-arsenical which is effective in treatment of early *T. rhodesiense* and *T. gambiense*, but is ineffective when the cerebrospinal fluid is involved. Surfen, Bayer 7602, alleviates the symptoms of Chagas' disease, due to *T. cruzi*. Congasin had a limited use in *T. congolense* infections in cattle.

Africa where the tsetse fly abets in maintaining a reservoir of *T. congolense* and to a lesser extent *T. vivax* in the indigenous animal population. *T. congolense* is refractory to arsenicals and other drugs effective in human trypanosomiasis but it has proved susceptible to chemotherapy with at least two members of the phenanthridinium group introduced by Browning, Morgan, Robb and Walls (1938). These quaternary compounds are known as "897" and "1553" or dimidium bromide. Both drugs are curative in a single parenteral dose and under certain circumstances may be prophylactic. Dimidium bromide is the more effective

drug and is administered in doses of about 1 mg./kg. (Hornby, Evans and Wilde, 1943, Carmichael and Bell, 1944, Crawshaw, 1947). Both drugs cause some liver damage, and photophobia, with photosensitization, has been observed with optimum doses of dimidium bromide.

### Trypanosome Drug-Resistance

It has already been noted that trypanosomes resistant to arspenamine and atoxyl are often sensitive to the similarly constituted arsenophenylglycin; these strains are also sensitive to arsenious acid, salvarsan, and foudadin, a fact attributed (Bär, 1941) to the exceptional avidity of the latter compounds for trypanosomes. Strains resistant to these compounds have seldom been found. It is claimed that increase in drug-resistance is frequently accompanied by increased sensitivity to other drugs.

### Drug Interference

Certain substances or groups of substances are known to interfere with the therapeutic action of arsenic and antimony compounds. They are (a) parafochsin, (b) certain redox systems, for example, pyrogallol and cysteine, and (c) potassium hexatantalate  $K_8Ta_6O_{19}$ . In the case of (a) and (c) the interfering action is delayed for four to six hours but (b) acts in a few minutes. One effect of (a) is to interfere with absorption of the drug while (b) stimulates respiration. The main effect of (c) seems to be to hinder the mobilization of the natural defensive mechanisms of the host.

The trypanocidal action of arsenicals, suramin and trypaflavin, but not tartar emetic, is increased by prior or simultaneous injections of gold compounds, a feature thought to be associated with the stimulation of phagocytosis.

### Mode of Action

It is the trivalent arsenicals which are the effective trypanocides and therefore the arspenamine type is oxidised and the trypanosomide type reduced. The same is thought to be true for the antimony compounds.

In contrast to the cells of the host the respiratory system of the trypanosome is insensitive to HCN but more sensitive to trivalent arsenic. The utilization of sugar is high, with production of lactic acid often sufficient to reduce the alkali-reserve of the host. Trypanocidal action is thought to interfere with glucose utilization or oxygen uptake (Jancso, 1936). It is also known that some redox dyes of suitable potential, some biological hydrogen-acceptors, and also some redox catalysts, protect trypanosomes from anti-trypanosome drugs. Examples are pyocyanin, a respiratory catalyst, methylene-blue, an H ion acceptor, ascorbic acid, and glutathione and cysteine. Volgtlin (1925) and Strangeways (1938), on the other hand, attributed the sulphhydryl effect to a direct action with arsenic, a belief which received indirect support from the respiration studies of Peters, Stoken and Thompson (1945).

It appears that suramin and the guanidines (synthalin) must have a different mode of action and are presumed to interfere with sugar metabolism at a late stage of utilization (Bär, 1941).

## ANTIBACTERIAL CHEMOTHERAPEUTIC DRUGS. I. THE SULPHONAMIDES

The amazingly productive development of antibacterial chemotherapeutic drugs in the space of 10 years, five of them war years, may be traced to two main causes. The first was the lone pioneering researches of the chemists and pharmacologists of the great Bayer organization, and the second the timely development of the studies on bacterial nutrition emanating from the Unit for Bacterial Chemistry (M.R.C.) led by Sir Paul Fildes. Contributory factors were the concurrent development of knowledge of the water soluble vitamins and of the nutritives of yeast. Domagk's (1935) discovery of the chemotherapeutic activity of prontosil rubrum against experimental infections due to *Streptococcus pyogenes* must rank as a very great discovery. It had all the explosive effects of a delayed action bomb. So little success had resulted from attempts to apply the classical chemotherapy of protozoa and spirochaetes to bacteria that in many quarters failure was presumed to be inevitable. Indeed, the slow development which characterized the use of mepacrine might well have been duplicated in the case of prontosil rubrum but for the careful work of Colebrook and Kenny (1935) in puerperal sepsis. The significance of this discovery could not be underestimated, and an explosive burst of industry resulted.

We must return to 1932 to witness the beginning. In that year Mietzsch and Klarer introduced the sulphonamido group to the dyestuff chrysoidin, which had been found by Eisenberg (1913) to be antibacterial in the test-tube. The richly deserved harvest of those who planned these researches was not reaped since by the investigations of Tréfouël, Tréfouël, Nitti and Bovet (1935) it was discovered that the dyestuff component of the molecule was unnecessary and the chemotherapeutic activity resided in the *p*-aminobenzenesulphonamide fragment afterwards known as sulphanilamide. This substance had been known chemically for many years.

Subsequent substituent groups in the amide group gave rise to sulphapyridine (Ewins and Phillips, 1938), bringing pneumococci within the scope of action (Whitby, 1938) then sulphathiazole (Herrell and Brown, 1939), and sulphadiazine (Fienstone, Williams, Wolff, Huntington and Crossley, 1940) widened the range to include staphylococci. Later sulphamerazine and sulphamezathine were added to the list. The structural relation of the sulphonamide drugs is shown in Fig. 6.

### Sulphonamide Activity in Intestinal Infections

Sulphaguanidine was proposed as an intestinal chemotherapeutic agent by Marshall, Bratton, White and Litchfield (1940) on the basis of experimental evidence that it was effective against *Shigella* species and was poorly absorbed. Sulphaguanidine was used in the Middle East early

# CHEMOTHERAPEUTIC DRUGS

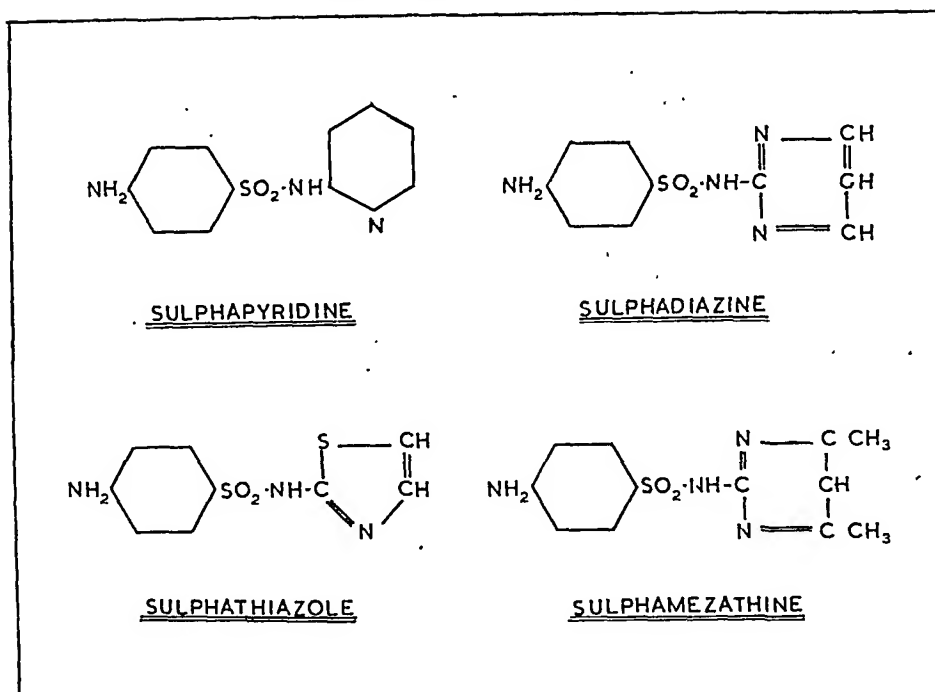


Fig. 6 (a). The derivation of sulphanilamide from prontosil and the chemical relation of the subsequently developed derivatives is shown in the figure.

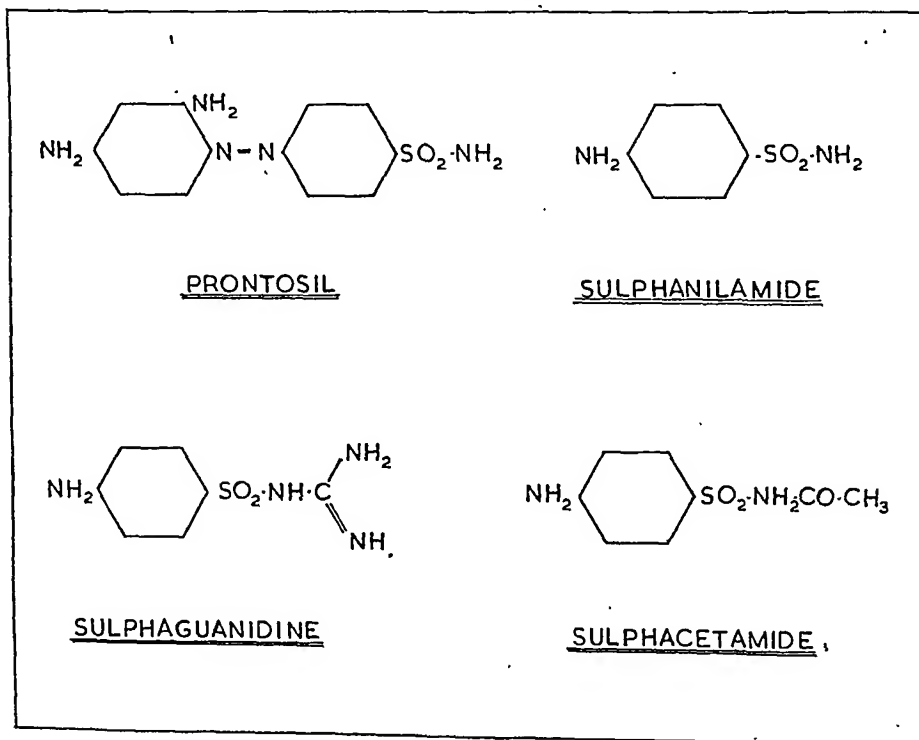


Fig. 6 (b).

in the war, and later in New Guinea with very favourable results (Fairley and Boyd (1945), Fairley (1945)). The clinical effectiveness of this drug appeared to endorse the theoretical conception that the full effect of the poorly absorbed drug should be felt within the lumen of the bowel. Yet it subsequently became known that equally good clinical responses could be obtained by drugs which were well enough absorbed to be effective agents in pyogenic fevers (Scadding, 1945), such as sulphathiazole and sulphadiazine. Considerations of this kind no doubt influenced the United States War Department, who eventually adopted sulphadiazine as the drug of choice in the treatment of bacillary dysentery (1944). It is now known that the allied sulphone derivative sulphetrone is freely excreted by the ileum, in addition to excretion in bile (Brownlee, Green and Woodbine, 1947), and it is possible that observations of a similar kind made with the freely absorbed sulphonamides would throw light on the problem.

Meanwhile, sulphasuxidine and sulphathalidine had been evolved; they are poorly soluble sulphathiazole derivatives slowly hydrolysed to give the active parent substance. The principles involved in their development illustrate their mode of action. The criterion of activity was the reduction in numbers of the coliform population of dog faeces after oral administration of the test drugs. They have been employed in surgery of the intestine (Poth, 1946).

### Metabolism and Excretion of Sulphonamides

The solubility of sulphonamides in body fluids becomes a significant problem because large doses have to be employed, at frequent intervals, to maintain an effective blood concentration. The position is complicated because a variable proportion of the sulphonamide drug is converted to its acetyl derivative which, in general, is less soluble in body fluids than the parent substance. In addition the drug and its acetyl derivative are much less soluble in acid than in alkaline urine. Care must be taken to keep the urine alkaline and to promote a diuresis. This is particularly important in tropical climates. Of sulphonamides in current use sulphathiazole is the least likely to cause crystaluria and sulphadiazine the most.

When sulphathiazole is used to treat urinary infections of *E. coli*, it is important first to promote a diuresis in order to reduce the coliform population since the efficacy of sulphonamides is related to the number of bacterial organisms exposed. For this purpose a sulphathiazole concentration of 0.5 mg. per 100 ml. is easily and safely maintained in an alkaline urine by 5 gm. daily with a fluid intake of three pints (Helmholtz, 1943).

### Mode of Action of Sulphonamide and Sulphone Drugs

The contribution which the Unit for Bacterial Chemistry (Fildes, 1946) made to the understanding of the mode of action of chemotherapeutic



ANTAGONISM OF SULPHONAMIDES WITH  
P-AMINO BENZOIC ACID.

RATIO OF SULPHONAMIDE; P. A. B.

SULPHANILAMIDE	1,600 : 1
SULPHAPYRIDINE	100 : 1
SULPHADIAZINE	100 : 1
SULPHATHIAZOLE	36 : 1

Fig. 7. The intrinsic efficiency of sulphonamide drugs is reflected in the ratio of inhibitor (P.A.B.) to drug.

drugs arose from the fundamental approach to bacterial metabolism and has already been noted. It culminated in a discovery of major import, namely the antagonism of sulphanilamide with *p*-amino-benzoic acid (Woods, 1940). The ratio of the inhibition of sulphonamide drugs with P.A.B. is shown in Fig. 6.

The studies in metabolism which made this concept possible may be briefly indicated. Pathogenic organisms differ in their capacity to build up the complex polypeptides of living processes, thus *E. coli* can synthesize its total polypeptide components from ammonia nitrogen, while *S. typhi* commonly requires tryptophane as a ready-made unit. Knight and Fildes (1933) stressed that "the parasitic or pathogenic habit is apt to be related to inability to synthesize tryptophane." The substances which bacteria cannot do without have been called "growth factors" by Fildes (1940). The synthesis of polypeptide requires energy derived from respiratory processes involved in the breaking up of simple sugars like glucose. This liberation is brought about by zymase, a combination of cozymase with protein. Cozymase is believed by Euler and Schlenk (1937) to consist of nicotinamide linked to pentose, three molecules of phosphoric acid, pentose and adenine.

Some strains of *Haemophilus influenzae* provide examples of an organism which require cozymase as a growth factor (A. and M. Lwoff, 1936),

while *H. parainfluenzae* requires the nicotinamide-nucleoside fragment only (Schlenk and Gengrich, 1942). Several strains of *Pasteurella* require nicotinamide as a growth factor and are unable to use nicotinic acid (Berkman, 1942) and *Staph. aureus* requires nicotinic acid (Knight, 1937). It will at once be appreciated how numerous must be the metabolic stages, each providing an opportunity for interference with the growth of the parasite. The "rational approach" to this goal was stated by Fildes (1940) in the following way. Chemotherapeutic drugs are considered to act by interfering with a metabolite essential for the parasite's growth; the drug exercises this interference-effect (i) by oxidizing a substance which requires to be reduced, or (ii) by molecular combination forming an inactive product, or (iii) by competition for an enzyme associated with the utilization of the metabolite by the parasite.

The third postulate visualizes the substitution of the chemotherapeutic agent for the structurally similar essential metabolite and the classical instance in chemotherapy was supplied by Woods (1940). The stage had been set by the discovery by Lockwood (1938) that the presence of peptone in a culture medium diminished the action of sulphanilamide. It was also discovered that this action could be inhibited by extracts from group C Streptococci (Stamp, 1939) and by body fluids (Green, 1940).

The conception of modifying the structure of an essential metabolite, so that it was no longer functional but would still occupy competitively the enzyme, was taken further by McIlwain (1940) who produced pyridine-3-sulphonic acid based on the model of nicotinic acid and sulphonamide. A second example, in the shape of pantooyltaurine, was provided by the same author (McIlwain and Hawking, 1943), who argued that this agent should be chemotherapeutic against hæmolytic streptococci infections by reason of its structural similarity to pantothenic acid. It proved to be so for rat infections, but not mice, and an explanation was afforded by the discovery of the high blood level of pantothenic acid in mice. The chemotherapeutic activity was not of practical importance but the principle was. It cannot fairly be claimed that the demonstration of preventing a parasite from utilizing a known metabolite, essential for its existence, altered radically the methods previously successful in the discovery of new chemotherapeutic agents. But it has added immensely to our understanding of the reason for success or failure.

### PENICILLIN

It is not possible in a short review of this kind to do more than indicate some of the more important aspects of the development and application of penicillin.

Interest in mutual antagonism between micro-organisms is as old as Pasteur's fundamental studies, but the many researches undertaken to-day in this field derived their impetus from the demonstration of the chemotherapeutic nature of penicillin by Florey and his collaborators (Chain, Florey, Gardner, Heatley, Jennings, Orr-Ewings and Sanders, 1940).

These observations, in turn, started with the inhibitory action of the mould contaminant observed by Fleming (1929). The singular freedom from toxicity of even grossly impure samples, when taken together with its catholic range of antibacterial and anti-spirochæte activity, distinguishes it as the most remarkably chemotherapeutic agent ever discovered.

The first samples of penicillin were obtained by surface growth and were isolated by charcoal absorption, charcoal elution and partition into weak alkali. Nowadays deep fermentation is used for growth and special methods have been developed for extraction and purification. On the chemical side it proved a tantalizing problem. Degradation gave two recognizable structures,  $\beta\beta$ -dimethylcysteine and an N-acylated glycine derivative. Synthetic studies and X-ray analysis suggested a structure unique in biologically active molecules—a  $\beta$ -lactam ring. Opening of this ring, by alkali, primary alcohols and amines, by thiol compounds, and by "penicillinase"—an enzyme derived from Gram-negative bacteria—inactivates the molecule. Minute yields of an antibacterial product having the biological characteristics of penicillin G were obtained by du Vigneaud and his collaborators (1946) in the products of synthesis but afforded no unequivocal proof of structure. Chemical modification in the attached side-chains have proved possible both by synthetic procedures and by adding chemical substances to the metabolism fluid. Four penicillins have been isolated from the products of growth and have the structure and nomenclature given to them in table I.

TABLE I

The four natural penicillins which have been isolated in quantity from the products of growth are known as I or F, II or G, III or X, and IV or K. They are distinguished by chemically distinct side-chains. Their antibacterial spectra are essentially similar.

PENICILLIN			% Activity (PEN. G = 100 per cent.)		
			S. aureus	St. pyogenes	Tr. pallidum
I,	F.	$C_5H_9$	90	82	53
II,	G.	$C_6H_5CH_2$	100	100	100
III,	X.	$OHC_6H_4CH_2$	55	140	50
IV,	K.	$C_5H_{17}$	140	120	75

#### Antibacterial Spectra

The antibacterial spectra of the four natural penicillins are essentially similar; the minor differences are shown in table I. The well-established superiority of penicillin II (G) for the treatment of syphilis over other penicillins, particularly IV (K) is due to the more rapid destruction and elimination of the latter in the body (U.S. Health Service, 1946).

#### Absorption, Degradation and Excretion

The extreme efficiency of penicillin, coupled with the limitations of biological tests for activity, has made precise estimates of its distribution

in tissue a question of conjecture rather than fact. A recent study of Rowlands, Rowley, and Stewart (1948), with radio-active sulphur-containing penicillin enables reasonably accurate deductions to be made about the fate of penicillin in cats. Introduced parenterally, penicillin is totally excreted by the kidney and, of this, only 30 per cent. is biologically active; given orally only one-third is absorbed and two-thirds remain in the gut. How much of the unabsorbed two-thirds is inactivated was not studied. These preliminary observations confirm the recent views of Bushby and Harkness (1946) that penicillin is slowly and incompletely absorbed from the gut.

The rapid rate of excretion of penicillin necessitates frequent injections and alternative devices have been sought to maintain tissue concentrations. These include (a) the use of very large doses, (b) the use of mechanisms to delay absorption, and (c) the use of drugs to minimise kidney excretion. Mechanism (c) is related to the fact that 80 per cent. of urinary penicillin is excreted by the tubules (Rake and Richardson, 1946). By simultaneously giving large doses of drugs which are also excreted by the tubules, penicillin excretion is delayed by competition. Examples of this largely theoretical use are diodone (Rammelkamp and Bradley, 1943), *p*-aminohippuric acid (Beyer, *et al.*, 1947), and sodium benzoate (Spaulding, *et al.*, 1947). Beyer, *et al.* (1947), ascribed advantages to "Caronamide" (carboxyphenylmethanesulphonanilide) which reversibly blocks excretion of penicillin, it is believed by enzymic inhibition, although itself excreted slowly only through the glomeruli.

Examples of mechanism (b) are the practice of chilling a limb before and after injection (Trumper and Thompson, 1946), the use of vasoconstrictors such as adrenalin (Parkins, *et al.*, 1946), and the admixture with beeswax and arachis oil (Romansky and Rittman, 1944). It should be noted that depot preparations, such as the Romansky depot, combine the principles of large doses and delayed absorption. An extension of the depot principle is the use of non-dissociating insoluble salts of penicillin in oil, in emulsion, or in methyl cellulose aqueous gels. An interesting example of this kind is procaine-penicillin which retains sufficient local anæsthetic properties to be painless on injection (Hobby, Brown, and Patelski, 1948; Robinson, Hirsh, Milloff, and Dowling, 1948). A disadvantage is that it inhibits the action of sulphonamide drugs by reason of its procaine content. New depots of this kind but without this disadvantage may confidently be expected.

### PURIFIED PENICILLINS

Allergic reactions which have been ascribed to impure penicillins have not been described with pure crystalline penicillin II (G). On this account there has developed a preference for the crystalline product especially for syphilis therapy and also for intraocular and intrathecal use. Of interest in this connection is the evidence of Hobby, *et al.* (1947), for the presence of an enhancing factor in impure penicillin. Thus, impure penicillin added

to crystalline G enhanced significantly the chemotherapeutic antistrep-tococcal effect of the latter, and the enhancing factor was present after treatment with penicillinase.

### Mode of Action

Penicillin is most active in the presence of multiplying bacteria in which it produces morphological changes ; these cells enlarge but do not divide. Observations of this kind suggest an interference with nucleic acid metabolism, and nucleic acid is said to reverse some aspect of penicillin activity *in vitro* (Pandali and Mariam, 1947). The specificity of penicillin against Gram-positive bacteria has directed attention to the nutritional requirements of these bacteria for certain amino-acids. It appears that glutamic acid, or glutamine, is brought within the cell by a system involving energy exchange which involves glycolysis (Gale, 1947). Penicillin interferes with glutamic acid assimilation so that the cell finally starves (Gale and Taylor, 1946). Pratt and Dufrenay (1948) also believe the failure to synthesize glutathione, because of non-assimilation of glutamic acid in the presence of penicillin, to be critical. Glutathione is thus not available to prevent the dehydrogenation of vital functional SH-groups by growth-preventing substances, and in this way the cell is regarded as collaborating in its own death.

### Distribution and Toxicity

Penicillin penetrates all tissues quickly and is found in wound exudates in the same or higher concentration as in blood. It readily passes the placental barrier, a most fortunate occurrence which, as we have seen, is applied to the treatment of syphilis of the unborn. It does not penetrate the blood-brain barrier and must be given intrathecally. By its use the prognosis of pyogenic infections is completely altered. Usually given parenterally, it may be given orally provided three to four times the parenteral dose is given. The oral route is useful for sensitive pathogens such as the gonococcus and the pneumococcus and particularly in the case of children. Inhalation of 100,000 units in a period of 20 minutes, three times daily, is satisfactory for pneumonia. Local application is effective.

### STREPTOMYCIN

Streptomycin is a product of the metabolism of some strains of *Actinomyces griseus*, a member of the aerial-mycelium producing group of the Streptomyces from which it takes its name. The selective Gram-negative antibacterial properties of the antibiotic were first described by Waksman and his colleagues in 1944. Two active strains were isolated from a heavily manured field and the throat of a chicken respectively; originally prepared by surface-culture the product is now obtained by deep fermentation.

### Antibacterial Spectrum

Included in its antibacterial spectrum is activity against staphylococci, streptococci, actinomyces, tubercle bacilli, *E. coli*, *S. typhi*, *Past. tularensis*, *K. pneumoniae*, *Br. abortus*, *Pr. vulgaris*, *Sal. schottmulleri*, *H. pertussis*, and

*Ps. aeruginosa* (Schatz, Bugie, and Waksman, 1944). It is therefore active in the test-tube against a number of pathogens not controlled by penicillin.

Animal experiments show streptomycin to be the most effective known chemotherapeutic agent for the control of experimental tuberculosis in the guinea-pig, which infection it will almost completely suppress under favourable conditions (Feldman, Hinshaw, and Mann, 1945). It protects mice infected with *E. coli* and *S. typhi*, but is less effective for this purpose than are the Polymyxins (Brownlee and Bushby, 1948). It is also effective in experimental infections due to *Past. tularensis* but not in *Br. abortus*.

### Chemistry

Two biologically active streptomycins have been isolated from the product of active strains. The substance formerly known as streptomycin A, and representing the major constituent, is properly called streptomycin. It is *N*-methyl-L-glucosaminido-streptosido-streptidine. The minor component is mannosido-streptomycin, formerly called Streptomycin B. It is represented as *D*-mannosido-*N*-methyl-L-glucosaminido-streptodido-streptidine; a "streptomycin residue" is also recognised which has antibiotic and enhancement properties (Waksman, 1948). The exact structure of streptomycin, designated *N*-methyl-L-glucosaminido-strepto-sido-streptidine of molecular formula  $C_{21}H_{39}N_7O_{12}$  is unknown. Hydrolysis yields streptidine  $C_8H_{18}N_6O_4$  and streptobiosamine  $C_{13}H_{23}NO_9$ , (Fig. 8) (Oswald and Nielsen, 1947; Folkers, Brink, and Kuehl, 1945).

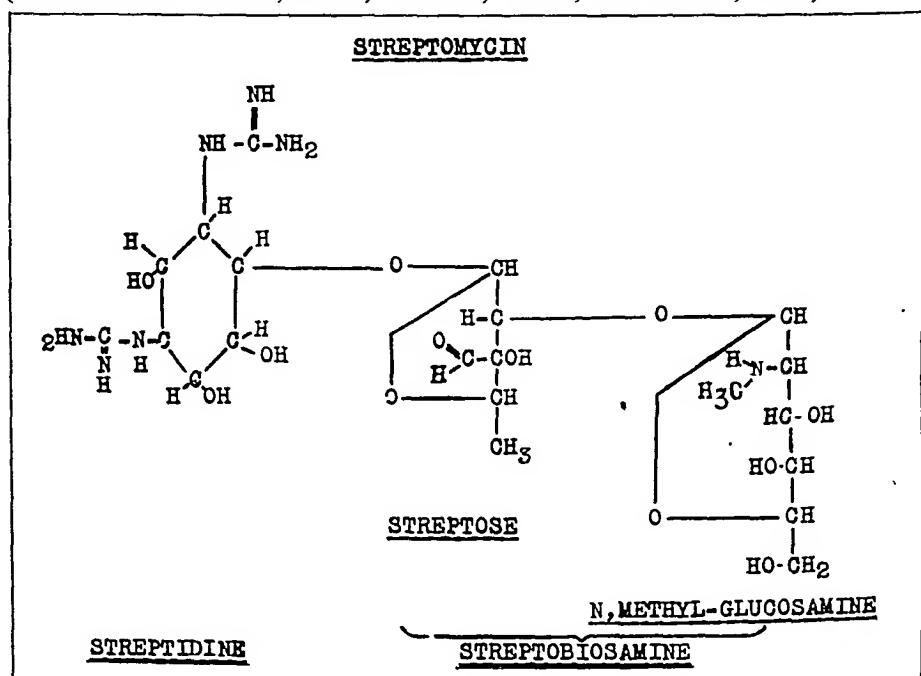


Fig. 8. Hydrolysis of streptomycin gives streptidine, which somewhat resembles a substituted inositol, and streptobiosamine. Streptobiosamine on hydrolysis gives a new sugar called streptose, and methyl-glucosamine. The complex is likely to be synthesized only with some difficulty.

Dihydrostreptomycin prepared by reducing streptomycin catalytically by chemical means is believed to be less toxic and likely to replace it clinically. Its activity is not reversed by cysteine or carboxyl reagents as is streptomycin.

### Mode of Action

The antibacterial action of streptomycin may be reversed in the test-tube by cysteine, hydroxylamine and 2-aminoethanthiol. Inactivation by cysteine may itself be reversed by iodine in chloroform, a demonstration which proves that sulphhydryl groups are not involved. Interesting evidence that streptomycin may be involved in an unknown metabolic system is supplied by the studies, made by Paine and Finland (1948), on development of resistance. In these experiments organisms were isolated which were dependent and could not grow without streptomycin. Thus in one population were (a) sensitive, (b) insensitive, and (c) dependent. The suggestion is made that streptomycin competes for the essential metabolite in (a), acts as a growth factor in (c) and is an essential metabolite, synthesized by the organism in (b).

### Absorption, Distribution, Excretion

Streptomycin is not absorbed when given orally. Given parenterally it is rapidly lost from circulating blood and from 50 to 75 per cent. is excreted in a biologically active form in the urine; some is known to be excreted in the bile. Thus injections must be made at three- to six-hour intervals. Unless very large doses are given it does not pass the blood-brain barrier (Heilman, Hinshaw, and Nichols, 1945; Elias and Durso, 1945). Depot preparations have not proved practicable, due, it is thought, to local destruction (Kolmer, Bondi, Warner, and Dietz, 1946).

### Toxicity

Apart from possible contamination with histamine-like depressor substances there is little evidence of toxicity at therapeutic levels with restricted courses of treatment of streptomycin of commercial purity. Danger of temporary or permanent damage to the 8th cranial nerve, resulting in vestibular dysfunction, is in direct ratio to the dose and duration of treatment (National Research Council, 1946). This danger is believed to be minimized by the use of dihydrostreptomycin. Pyrexia, dermatitis, conjunctivitis, flushes and allergic reactions have been recorded. There has been occasional sensitization in nursing staff.

### Resistance

The rapidity with which organisms develop resistance to streptomycin *in vitro* and *in vivo* constitute its greatest disadvantage. Concurrent with the acquisition of resistance there is no loss of virulence.

### Clinical Uses

Streptomycin is the most effective known anti-tuberculous drug but because of the rapid development of resistance its uses are restricted to

certain forms of management. These are tuberculous meningitis, miliary tuberculosis, endobronchial and laryngeal lesions, and the topical application to ulcers (Keefer, Blake, Lockwood, Long, Marshall, and Barrywood, 1946). Some authors consider it dangerous to exhibit the drug where there is caseous disease or where glands are involved (Brownlee, Madigan, Swift, and Payling Wright, 1947). A new development of some promise has been the evolution of combined streptomycin and sulphetrone therapy. Sulphetrone is a diamino-diphenylsulphone derivative of low toxicity. The two anti-tuberculous compounds were shown by Brownlee and Kennedy (1948) to be synergistic in the experimental animal and they have been applied to the existing streptomycin field in the hope of establishing a better recovery rate and also to attempt to extend the range of usefulness of streptomycin (Brownlee, Madigan, Swift, and Payling Wright, 1947).

Doses currently employed by parenteral injection range from 0.2 to 2 g. daily, given twice daily for 12 weeks. Intrathecally 100 mg. combined with 200 mg. of sulphetrone is given once daily; sulphetrone parenterally or orally to give a blood concentration of 7.5 mg. per 100 ml. is also used.

In other than tuberculous infections streptomycin has proved effective in tularemia, and in meningitis due to Gram-negative infections.

### OTHER ANTIBIOTICS

One hundred and thirty-three distinct antibiotic substances from bacteria, fungi or plants are described (Antibiotic Substances, 1948), but few of these have proved acceptable for medical use mainly because of toxicity or because their antibacterial field of activity is adequately controlled by an existing drug, for example, penicillin.

#### Subtilis Group

Organisms of the subtilis group have provided several antibiotics, one of which is bacitracin (Johnson, Anker, and McLeney, 1945). It is effective chemotherapeutically in streptococcal and clostridial infections but is nephrotoxic. It appears to have a use as a local antibacterial agent. A second example is subtilin which is reported to be chemotherapeutic against Gram-positive and tubercle bacteria. Its status is unknown but it has been used by local application (Anderson, *et al.*, 1946). Of more immediate interest are three antibiotics active against Gram-negative organisms. They are the polymyxins, chloromycetin and aureomycin.

### THE POLYMYXINS

Five closely related but chemically and pharmacologically distinct polymyxins have been prepared from five different strains of *Bacillus polymyxa*. The antibiotic at first called "Aerosporin" and now known as polymyxin "A" was discovered at The Wellcome Research Laboratories in the course of routine screening of possible antibiotics in 1945. Isolated by Ainsworth, Brown, and Brownlee (1947) it was shown to be chemotherapeutic and selectively active against Gram-negative pathogens.



Subsequently, its chemotherapeutic and pharmacological properties were described by Brownlee and Bushby (1948); after the latter paper had been lodged for publication the report on "Polymyxin" by Stansly *et al.*, (1947) became available. This antibiotic is now known as Polymyxin "D" (Brownlee, 1948). There is an even earlier report of the antibacterial nature of crude liquid cultures of *Bacillus polymyxa* by Benedict and Langlykke (1947), the antibacterial properties of which are now known to be due to polymyxin "D" (Brownlee, 1948). The commercial production of Polymyxin "E" is now made by deep culture methods.

### Antibacterial Spectrum and Chemotherapeutic Activity

The polymyxins are remarkably potent, selective, antibiotics, active against Gram-negative pathogens. In animal experiments they are the most effective known chemotherapeutic agents against infections with *E. coli*, *S. typhi*, *K. pneumoniae*, and *H. pertussis*.

### Chemistry

Five chemically distinct polymyxins, A, B, C, D and E, have been described. All are basic peptides, yielding on acid hydrolysis, three amino-acids in common, namely leucine, threonine and diaminobutyric acid together with an unidentified optically active fatty acid of formula  $C_9H_{18}O_2$  (Brownlee and Jones, 1948)\*. A summary of the amino-acid components (Jones, 1948) together with a note of important pharmacological differences (Brownlee, 1948) is given in table II.

TABLE II.

Differences in the amino-acid composition and the pharmacological properties of the polymyxins.

	POLYMYXIN				
	A	B	C	D	E
Leucine .. .. .	+	+	+	+	+
Phenyl-alanine .. .. .	—	+	+	—	—
Threonine .. .. .	+	+	+	+	+
Serine .. .. .	—	—	—	+	—
$\alpha$ -Diamino-Butyric Acid .. .. .	+	+	+	+	+
Fatty Acid $C_9H_{18}O_2$ .. .. .	+	+	+	+	+
Nephrotoxicity .. .. .	+	—	+	+	—
Myonecrosis .. .. .	—	+	+	+	—

### Properties

The polymyxins are bases insoluble in water whose salts are extremely soluble yielding stable solutions when pure. They may be standardized biologically through reference standards of the polymyxin in question, by dilution or plate assay, using *E. coli*, *S. paratyphosa* or *Br. bronchiseptica* or, probably chemically, by estimation of their amino-acid

\*Now identified as *d*-6-methyl octan-1-oic acid. Wilkinson, S. (1949) *Nature*, 164, 622.

content (Short, 1948). The polymyxins are not inactivated by known enzymes, and their precipitation as insoluble soaps, their only known inhibitory reversal, provides the only clue to their mode of action. Given orally they are not absorbed and this may be used to eliminate the Gram-negative flora of the gut; by the parenteral route they are rapidly lost to the circulating blood, but little is excreted in urine in a biologically active form; there is evidence of an additive effect with repeated doses, and excretion continues after cessation of dosage. It does not pass the blood-brain barrier, and is not excreted in bile. Unlike streptomycin, drug-resistant strains may be developed only with great difficulty.

### Toxicity

The nephrotoxicity of polymyxins A, C and D precludes their clinical use. Polymyxin B is free from nephrotoxicity, but specifically damages muscle at the injection site; polymyxin E is free from both defects and is the antibiotic of choice for clinical trial.

### Clinical Use

Polymyxin E is at present the subject of extensive clinical evaluation in whooping-cough, in gastro-enteritis in children, in enteric fevers, and in local application to infected wounds and burns. It is also being observed in Gram-negative pyogenic infections and meningitis.

### CHLOROMYCETIN

The isolation of crystalline chloromycetin from submerged culture of *Streptomyces venezuelæ* (Ehrlich, *et al.*, 1948) has been described (Bartz, 1948). Its antibacterial spectra include in its range *S. typhi*, *S. dysenteriae*, *K. pneumoniae*, salmonella and proteus, and of greater significance, it is active against rickettsiae and the viruses of lymphogranuloma and psittacosis (Gotlieb, *et al.*, 1948, Smith, *et al.*, 1948). It has proved curative in man infected with *scrub typhus* (Chloromycetin editorial, 1948). It is active when given by mouth and is a molecule of relatively low molecular weight which contains chlorine. When its structure becomes known there may be provided the much-sought-for clue to synthetic antiviral chemotherapeutic agents.

### AUREOMYCIN, DUOMYCIN

Aureomycin is produced by *Streptomyces aureofaciens* a new species of actinomyces isolated from soil (Bryer, *et al.*, 1948). It has been produced as a crystalline hydrochloride.

Its antibacterial spectra covers both Gram-positive and Gram-negative organisms and in addition to tubercle bacilli, are included fungi, rickettsiae and viruses. Favourable clinical comment has been made in Rocky Mountain spotted fever, marine typhus, Q fever, scrub typhus, psittacosis, lymphogranuloma venereum, Gram-negative urinary infections, brucellosis and typhoid. Ocular infections, with staphylococci, coli, and of epidemic keratitis and trachoma responded favourably.

Its acute toxicity is low orally or by injection. It is excreted quickly and injections every three hours are necessary to obtain therapeutic blood levels. It does not pass the blood-brain barrier. A hypochromic anæmia, controlled by folic-acid and iron, appeared in some cases given 10 to 40 mg. daily intramuscularly for eight to 31 days.

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# VISCERAL ACTINOMYCOSIS

Bradshaw Lecture delivered at the Royal College of Surgeons of England

on

10th November, 1949

by

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MR. PRESIDENT, MEMBERS OF COUNCIL, Ladies and Gentlemen, I wish first to express my sense of the honour conferred upon me by being asked to deliver the 68th Bradshaw Lecture at this College, and particularly to thank the retiring President, Lord Webb-Johnson, with whom lay the nomination for this privilege. The subject I have chosen has never previously been discussed in any lecture in the series, yet for a reason which I shall give you I think it would have been of special interest to Dr. Bradshaw. Dr. William Wood Bradshaw became a Fellow of this College in 1854. For many years he was in practice in Andover and later in Reading, and he was at one time Vice-President of the Reading Pathological Society. He died in 1866, and his widow, Mrs. Sally Bradshaw, by a Will dated September 6th, 1875, left money to found a Lectureship whereby the memory of her husband might be perpetually honoured (Fig. 1). This Will was proved on August 26th, 1880. Between these two dates something interesting had happened—*Actinomyces* had been discovered and the disease *Actinomycosis* named. The discovery was made by Bollinger in 1876, and the name was coined by his friend Harz. Now Dr. Bradshaw did not publish many clinical articles, but if you turn to the *Lancet* for 1846 you will find that he published a remarkable account of a case of abdominal abscess. The description was of a slowly developing hard mass in the right iliac fossa culminating after two years in an abscess which was opened. The patient improved under treatment by potassium iodide, but again relapsed and the right thigh became permanently flexed. The patient's general condition deteriorated and there was a fatal issue. From the account given there can be little doubt that this was a case of *actinomycosis*, a disease which was unknown at the time when the article was published. The first case to be noted in man was by Ponfick in 1879, so that by the time Mrs. Bradshaw's Will was proved *actinomycosis* had been added to the list of diseases affecting human beings. A most excellent clinical account of the disease was published by Israel in 1886.

For many years our knowledge of the *actinomyces* which causes disease in man and animals remained insecure, but a series of careful observers—Wolff, Homer Wright, Naeslund, Colebrook and others established certain facts which even now are not sufficiently known. *Actinomyces* constitutes a group of common organisms frequently found in the soil. Most of them are aerobic and seldom cause pathological lesions in man.

may escape into the cellular tissues and begin to grow, well away from the surface. The extraction of a tooth or a perforation of the appendix will be sufficient to allow its escape. The tissue reaction exceptionally is acute and may form an abscess in which the fungus grows plentifully but not in the form of granules. More commonly the reaction leads to the formation of a mass of hard fibrous tissue, almost avascular and on section looking very like a sarcoma or scirrhous carcinoma; embedded in this may sometimes be seen small abscesses, but in many cases it needs very careful microscopic examination to find any trace of the organism. Sooner or later softening occurs and an abscess is formed in which the granules are present. The inflammation spreads by continuity and often follows the line of least resistance; it has little respect for any tissue, always excepting surface epithelium and dense fascia such as the dura mater.

The dense fibrous reaction of the undifferentiated mesenchyme cells, its chronicity and avascularity, give rise to some problems and furnish material for reflection. How is it that such minute portions of the actinomycetes can lead to the formation of such a mass of tissue which is sometimes almost like cartilage? There must be some powerful irritant or stimulator. Whence does it come? Twenty-five years ago Carrel taught us that fibroblasts were maintained in a true state of cultivation only by embryonic tissue juice or extracts of some adult tissues or of leucocytes. But the only element which is peculiar to the actinomycotic reaction is the actinomycetes and it is difficult to escape the conclusion that the stimulator of the mesenchyme cells comes from some degenerative or secretory product of the organism itself. We now know that several of the fungi can produce substances of immense power—witness actinomycin, streptomycin and penicillin—and it seems reasonable to assume that the extraordinary stimulus for fibrous tissue formation comes from the actinomycetes. There is an interesting sidelight on this view. Clinically, we know that treatment by X-rays may cause a softening of this hard fibrous tissue and when we recall the statement of Carrel that the substances which he found promoted the growth of fibroblasts and were sensitive to the X-rays and to radium, we may be right in concluding that the softening process may be the consequence of the destruction of the stimulating substance, which provokes the formation of fibrous tissue.

Another problem—how is it that the actinomycetes can remain latent in the tissues for months or years? In the first place being micro-aerophilic it can maintain its existence in avascular tissue. Then there is little doubt that the arrangement of the small foci of the fungus in the tissues—growing hyphae surrounded by a palisade of clubs—is beneficial and protective. Thirdly, the conglomeration of the fungus into granules gives added protection. Some recent very interesting work of Per Holm supports this view. He found that suspensions of pathological actinomycetes were as sensitive to penicillin as staphylococci, but it required much more penicillin to destroy the organism when it was collected into

in which the organism was seen on microscopic examination at the site of a perforation (Fig. 2). When once it has reached the peritoneal cavity it may cause a subphrenic abscess, may invade the liver, or may even gravitate to the pelvis and form a tumour there (Fig. 3). The intestinal contents pass quickly along the small bowel, and it is very rare



Fig. 2 Actinomycosis of the duodenum.

(Reprinted from *Actinomycosis* by V. Zachary Cope, Oxford, 1938.)

for the actinomyces to cause any lesion there, though a remarkable instance has been recorded by Sir Gordon Gordon-Taylor. The vermiform appendix, however, provides a comfortable home, and at the same time offers a chance of its escape so that perforative appendicitis is far the commonest precursor to abdominal actinomycosis. In a number of recorded cases the perforation of the appendix has communicated directly with sinuses in the inflammatory mass. When once the process has started the lesion may extend by contiguity downward into the pelvis, backward into the psoas muscle, upwards towards the kidney and medialwards to the vertebral column (Fig. 4). The liver may be attacked by contiguity or by portal infection. The best demonstration of this remarkable method of spread is seen in the case which was under the care of Sir Heneage Ogilvie (Fig. 5); in this case when a sinus in the right iliac region was injected with an opaque solution and was X-rayed, there resulted a picture showing that the sinus communicated directly with tracks which ramified in the liver, traversed the diaphragm and were directly connected with the bronchioles in the right lung.

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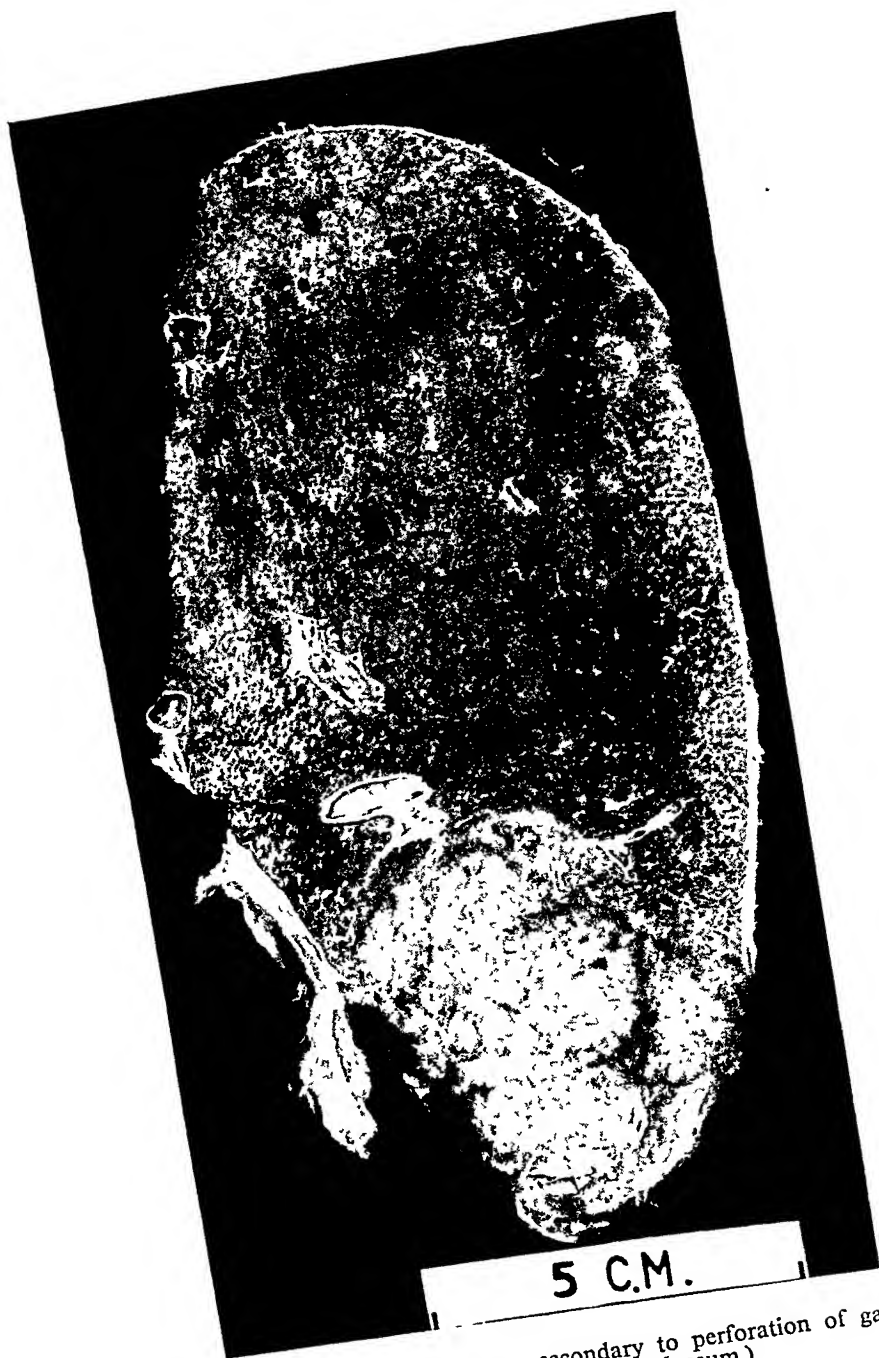


Fig. 3. Actinomycosis of the liver, secondary to perforation of gastric ulcer.  
(St. Mary's Hospital Museum.)



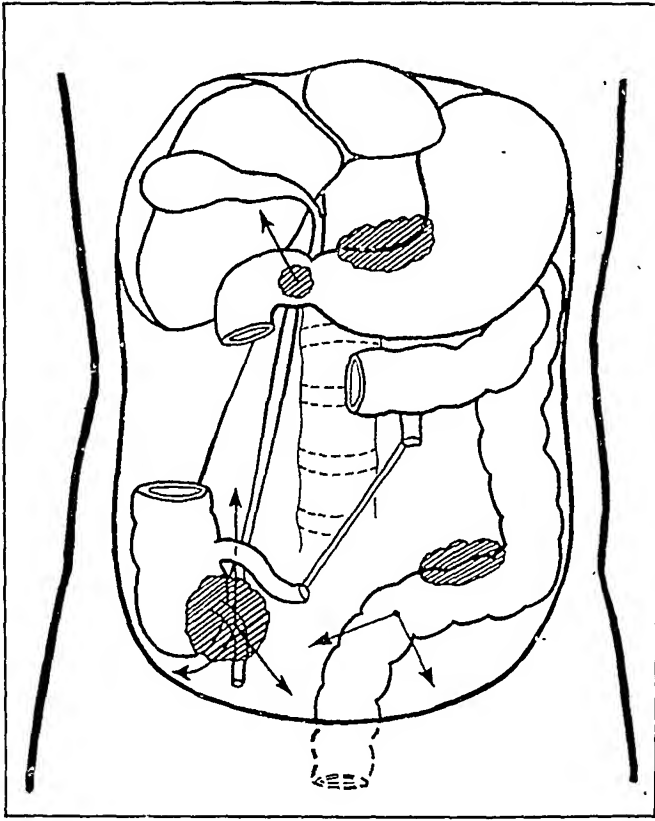


Fig. 4. Diagram of common sites of abdominal Actinomycosis with arrows indicating lines of extension.

The colon and rectum are not so commonly affected, but quite frequently enough to make it necessary always to consider this disease as a possibility in discussing the diagnosis; in nearly every case there develops an abdominal or pelvic tumour which usually simulates a malignant growth, and in several cases has been excised with that pre-operative diagnosis.

Thoracic infections are also due to spread of infection from the mouth (Fig. 6). This may result in several ways. A rare accident, but one which befell a former distinguished member of the Court of Examiners of this College, is the accidental falling of an extracted carious tooth into one of the bronchi; in the case referred to, which was under the care of Dr. Maurice Davidson and the late Mr. Roberts; an actinomycotic abscess formed in the lung round the tooth, and this needed open drainage for its cure. More often minute portions of the fungus are aspirated into the bronchial tree where they may persist sometimes in a bronchiectatic cavity or in some small inflammatory focus. This view has recently received remarkable confirmation. Two years ago



Fig. 5. X-ray of thorax and abdomen after injection of iliac sinus. (Sir Heneage Ogilvie's case.)

E. B. Kaye published some illuminating facts giving the results of his investigation of 240 consecutive patients treated for broncho-pulmonary infections. He bronchoscoped them all, and took cultures of the sputum and of the bronchial secretions. In 65 of these cases, which included examples of pneumonitis, lung abscess, bronchiectasis, aspiration pneumonia, suppuration distal to a bronchial carcinoma, and simple bronchitis, he was able to isolate and to culture the actinomyces *Israelii*. The wonder is that pulmonary actinomycosis is comparatively rare, for the microbe is so often there merely awaiting the chance to invade the tissues. In any case we have a simple explanation of the disease when it invades the parenchyma of the lung. But when it starts in the mediastinum, as it often does, we must seek another route of infection, and most likely this is by the escape of the organism through the œsophageal wall. We cannot watch this process, and, as in the cheek, the organism leaves little or no trace of the route by which it escaped, but clinically this method of infection fits in best with the facts; frequently an empyema is the next stage, and then the lung may become involved. It is the rule for pulmonary actinomycosis to invade the thoracic wall and come to the surface, quite unlike tuberculosis.

The thorax sometimes becomes infected through the bursting of an hepatic abscess through the diaphragm, or it may become involved by a low cervical infection descending into the superior mediastinum.

The cranial cavity may be affected by infection spreading up from the face through the basal foramina, or the brain may be infected via the blood stream. There is in addition a very remarkable single lesion

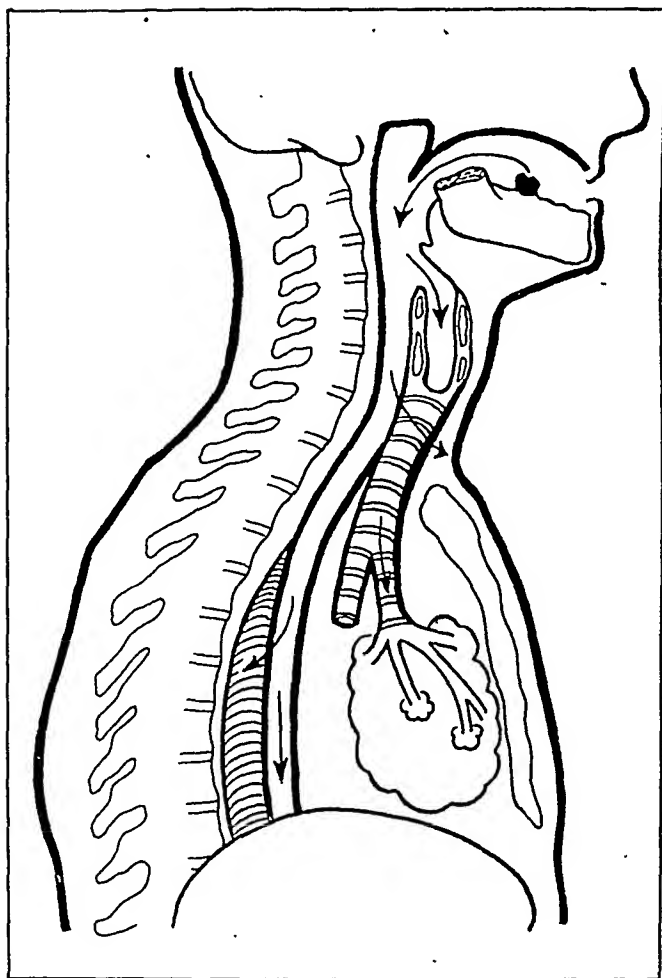


Fig. 6. Diagram indicating how Actinomycosis infects the thorax.

which has occasionally formed in the region of the septum lucidum or third ventricle; this consists of a filbert-sized actinomycoma which occurs without any other trace of similar infection discoverable in the body. Till recently only six of these extraordinary solitary lesions had been described, but four years ago a seventh—a pedunculated tumour in the third ventricle—was recorded by T. G. Orr. I have previously stated, and still think, that in these rare cases infection travels up from the upper meatus of the nose via the sheath of the olfactory nerves.

The vertebral column may be involved either in abdominal or thoracic actinomycosis, but the spinal cord itself is rarely involved.

The vertebral column is affected in a way quite different from that in any other form of infection. The process commonly affects the bodies and transverse processes, but it may invade any part with which

it comes in contact. There is a very slow process of absorption, and a simultaneous formation of new bone, which maintains the framework and strength of the bodies so that collapse of a vertebra is rarely seen and is never so complete as in tuberculosis. The intervertebral discs are involved late and often hardly at all, and the manner of their involvement is different from that in tubercle. The disease may surround the exits of the nerves and cause severe pain, but it is rare for the fungus to penetrate the spinal dura. The X-ray picture of vertebral actinomycosis is often pathognomonic, for the side view of the bodies gives one the impression of a coarse sieve, each opening being surrounded by a circle of denser bone (Figs. 7 and 8).

### Symptoms

How is it possible briefly to enumerate, still less describe, the symptoms caused by visceral actinomycosis? It would require a short text-book to do so. In the early stages in any part there is nothing at all characteristic. The onset may be acute, subacute or insidiously chronic. Irregular fever is the rule, and there is moderate leucocytosis. Whenever the condition has existed for some time there will be increasing anæmia, lowered serum protein, wasting and loss of strength. Pain may be absent or very severe, particularly if the vertebral column be attacked.

The local symptoms vary greatly according to the part affected. In the abdomen there is usually the formation of a hard swelling which is significant when it forms around the sinus left by the drainage of an appendicular abscess. When such a tumour develops in the pelvis or around the colon without any previous warning it is usually taken for a malignant growth, although it seldom causes acute obstruction. In the liver, which it may reach via branches of the portal vein or by direct contact, it may take the form of one or more localized tumour-like masses, or it may invade a large portion of one of the lobes and lead to the formation of large abscesses which disintegrate the glandular substance. I have known at least two cases in which fairly small localized masses in the liver were impossible to diagnose until a portion had been removed for biopsy. Hepatic actinomycosis may lead to subphrenic abscess and pleural effusion.

When actinomycosis attacks the contents of the thorax it may closely simulate tuberculosis, pneumonitis, pleural effusion, empyema, or malignant growth; when it invades the mediastinum it may look like a mass of glands, or when the vertebræ are involved simulate osteomyelitis, or give rise to meningeal symptoms. Wherever it may penetrate, the actinomycotic process, sooner or later, always softens in one part or another and forms an abscess which generally comes to the surface of the body, often some way from the main focus. Such an abscess differs from that due to tuberculosis in that it is generally painful, causes redness and œdema of the skin and adjacent parts, and contains a thicker pus, from which the granules can usually be obtained.

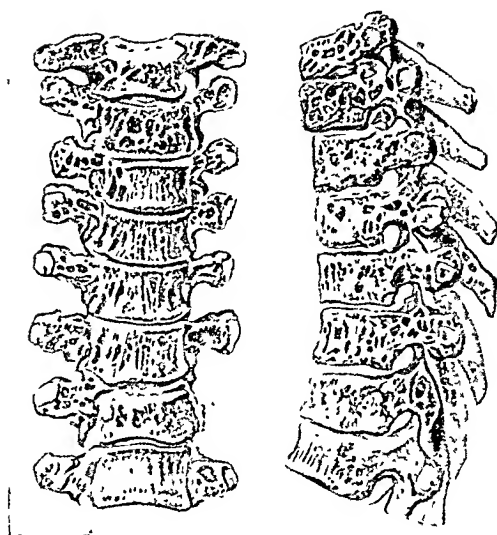


Fig. 7. Effect of Actinomycosis on the vertebræ. (From Poncet and Bérard, *Actinomycose Humaine*, 1898, after Boström.)

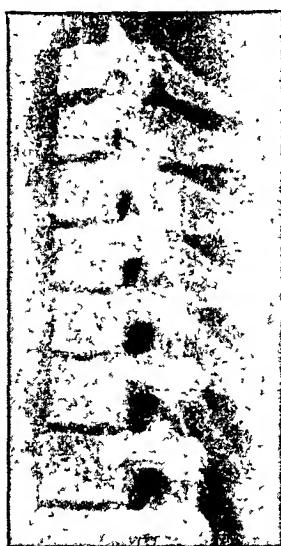


Fig. 8. X-ray of cervico dorsal region affected by Actinomycosis. (Specimen at St. Mary's Hospital Museum.)

You will now understand why there are no characteristic symptoms. Visceral actinomycosis has a definitely ugly face but wears many deceptive masks. So many clinical pictures but always the same insidious disease. One must, therefore, always consider the possibility of this disease.

### Diagnosis

Even when one does consider its possibility there remains the difficulty of differential diagnosis. Actinomycosis might well be called the "most

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misdiagnosed disease." I know no disease which is so often missed by experienced clinicians. Too many cases are diagnosed for the first time at autopsy. It is the rule for visceral actinomycosis to pursue its course for many months, sometimes for a year or two, before the possibility of its presence occurs to the observer. There are several reasons for this. First, we have no reliable reaction or blood-test for the disease. Agglutination, complement fixation, estimation of the opsonic index, a precipitin test, and a cutaneous reaction have all been tried and advocated, but Naeslund who tested them all found none reliable. Secondly, in the case of deep visceral lesions it may be months before an abscess comes to the surface from which the organism may be obtained. Moreover, it requires care and time to culture actinomyces, which soon dies if the pus dries, and the organism takes a much longer time to grow than the usual septic organisms. I purposely repeat that a final and important cause is that the disease may not be on the list of possible diagnoses which the observer goes through as a routine. The incidence of diseases has so altered through the last 40 years that (in my experience at least) it is now more common to meet with actinomycosis than with a syphilitic gumma.

The differential diagnosis has to be made from other causes of acute and chronic inflammation and from malignant growth. Syphilis may be excluded by the Wasserman reaction or other specific test. Tuberculosis and malignant disease of the lung cannot always be differentiated until an abscess has formed. The lesions in the intestine may closely simulate cancer for there are many clinical resemblances. Both are frequently insidious in origin and prolonged in development, both advance inexorably into the neighbouring tissues and in neither case is much respect paid to the nature of those tissues except in the case of lymphatic glands. In each case hard tumours may be formed. Finally, even microscopic examination may not reveal the fungus unless many sections are examined, and the fibrous tissue reaction has sometimes led to the diagnosis of fibro-sarcoma.

Since certain diagnosis can only be made by finding the actinomyces in the pus or tissues, it is clear that there should be the closest co-operation between the pathologist and the clinician in diagnosing this disease. The surgeon's task is not finished when he opens the abscess; he fails in his duty if he does not call the pathologist into consultation.

### Treatment

During the past 10 years the treatment of actinomycosis has changed remarkably for the better and visceral infection, which gave a mortality of more than 50 per cent., has now had to submit to a degree of control or even cure which was previously impossible. Much of the treatment used in 1939 is now out of date, although some books still insert them. Copper sulphate, formalin, salvarsan, thymol—all formerly advocated by some—have been superseded by the sulpha-drugs, and the antibiotics.

There is little need for vaccines, and X-rays are not so often needed therapeutically, though still of value in diagnosis. With the possibility of cure has come the fuller realization that visceral actinomycosis has a serious effect upon the general health and that constitutional treatment is very important. Amyloid disease is recognized as a serious complication.

Constitutional treatment consists in giving a plentiful and nourishing diet and carrying out the same rules with regard to fresh air and sunshine as in tuberculosis. Extra milk should be provided and the anæmia treated by hæmatinics or, if necessary, by transfusion. In no case should any operative measures be undertaken before the general strength has been built up.

With regard to drug treatment, iodine and its derivatives are still of value in promoting absorption, but potassium iodide is not a specific and need never be given in large doses. The best method of administering iodine is that of Chitty, who recommends five minims of tinctura iodi in a glass of milk thrice daily.

The discovery in 1935 by Domagk that prontosil red could cure streptococcal infection in mice led to its use in streptococcal and other infections in man. In 1937 Poulton of Guy's tried it in a case of streptococcal infection complicating a case of actinomycosis, and the patient improved greatly; the improvement, however, was attributed to the effect of the drug on the streptococcal infection. The following year, a young officer in the R.A.M.C., by name Oliver Walker, was faced at Millbank with the case of a soldier suffering from actinomycosis following perforative appendicitis; there was a hard lump surrounding a right iliac sinus, and no benefit had accrued under treatment by potassium iodide and thymol. On this case Walker tried the effect of one gram of sulphanilamide three times a day for two periods of five days, and he was gratified to find that the whole condition rapidly got well. He reported his success in a short and inconspicuous note in the *Lancet*. This report encouraged two doctors at Cook County Hospital, Chicago (Miller and Fell) to report a similar case which they had independently treated successfully by the same drug. Soon many other cases were reported by Hall, Ogilvie, Dorling and Eckhoff, and it became established that several of the sulpha group of drugs had a definite beneficial effect on actinomycosis. In 1941 it was shown by Cutting and Gebhardt that sulphanilamide, sulphathiazole and sulphadiazine had a definite inhibiting effect on the actinomycetes in vitro.

Very soon after this a still more powerful therapeutic substance was introduced into surgery—a substance discovered by a Fellow of this College. Forty years ago this last June, as I was waiting with trepidation for the result of the examination for the Fellowship of this College I saw go into the Library in front of me to receive his Diploma of Fellow a young doctor called Alexander Fleming, who, needless to say, had passed at his first attempt. After gaining his Fellowship, Fleming retired

to work in the pathological laboratory and one feared that he might be lost to surgery. But he retired only to do greater things for surgery, for no single discovery in this century has so improved the possibilities of surgery as the discovery of penicillin in 1929. When, during the war, Florey and Chain purified this substance and showed more clearly its clinical possibilities, it was not long before its effect on the actinomyces was demonstrated. One of the first series of clinical trials by Florey was a case of empyema, in which a streptothrix was found; treatment by penicillin in comparatively small doses caused the disappearance of the streptothrix from the discharge. Since that time penicillin has been used more extensively for the treatment of actinomycosis, and as the supply became more plentiful greater doses were given and better results obtained. In 1947 Nichols and Hewett reviewed 98 cases of the disease, of which 45 were treated by penicillin and 53 without it. The period of disability caused by the disease was shortened by penicillin and was most striking with visceral actinomycosis. This is shown in the figures they quote :—

Pulmonary	with penicillin	5, with disease, retarded. 4 failures.
	without penicillin	13, of which only 1 improved.
Abdominal	with penicillin	7 of which 5 were cured.
	without penicillin	14 of which 9 died, 4 were still ill and 1 recovery.
Pelvic	with penicillin	3 all cured.
	without penicillin	1 not cured.

In reading through the case reports from year to year certain facts stand out clearly. At first, short courses of comparatively small doses were given; improvement occurred, but did not prove lasting, so that repeated courses of treatment were required. Later, when doses became bigger, the results were much better and cure was sometimes attained. Often, however, recurrence took place after an interval of some months. It then became evident that for severe cases of visceral actinomycosis it was necessary to give large doses of penicillin for long periods of time, without intermission. That, at least, has been my personal experience.

That it has been the experience of others may be judged by their published writings. In 1946 Decker laid it down that "penicillin should be given in large doses, 100,000 to 200,000 units per day for 10 to 14 days. After several weeks' rest repeated courses of the treatment over 12 months or at any time of recurrence." Two years later, in 1948, other observers—Nichols and Herell—found that the dose given to their patients varied from 800,000 to 1,000,000 units daily, and was continued for from two to seven weeks; they concluded that the dosage should be at least half-a-million units daily, and should be continued for at least six weeks. It is true that many cases get well with less than these amounts, particularly abdominal cases, but in difficult thoracic lesions it will be found that these doses are on the low side and at least a million units daily will be needed.



Short courses of treatment with penicillin are unsatisfactory, for their recurrence is the rule. There should be no intermission until the patient has been free from symptoms for some weeks or months. This has been well recognized by Adamson and Hagerman, who last year reported a case of successfully treated pulmonary actinomycosis by penicillin and sulphadital—"thus, when dealing with pulmonary actinomycosis, the most appropriate procedure seems to be chemotherapeutic treatment continued until long after the clinical symptoms have subsided."

This is no place to discuss the methods of giving the penicillin, but my own preference is for giving two large and concentrated doses by intramuscular injection twice in the 24 hours. Three-hourly injections may be a great trial to the patient, and the intravenous method is not so convenient and does not give better results.

In cases in which the response to penicillin is slow or absent there may be some advantage in combining it with one of the sulpha group of drugs. Many observers have claimed better results by the combination of the two drugs. Certainly one of the few recorded cures of actinomycosis of the liver was treated by the combination of penicillin with sulphamerazine (Bonney). In some of the recorded cures by the combined method the doses of penicillin were much smaller than would be considered necessary nowadays.

For those cases which do not respond to treatment by penicillin other antibiotics are available. Two years ago Costigan found streptomycin of benefit in a case of cervico-facial actinomycosis, and last year Keefer and Hewitt found it had a beneficial effect in a case of abdominal infection. This year Torrens and Wood, and also Pemberton and Hunter, also proved its value in abdominal actinomycosis. The former gave two grams a day for a month, and then reduced the dose to one gram daily for a further period; the latter gave one gram daily for a month and let the patient take the drug by mouth. Usually the drug is given parenterally for it is only slightly absorbed from the intestine. It cannot be continued for such long periods as penicillin without risk of toxic symptoms. Penicillin and streptomycin should not be given together, for the latter has a deleterious effect on the action of penicillin. There is another antibiotic—bacitracin (Meleney)—which has also been proved to have some curative power in actinomycosis, but this drug is not yet available in this country.

Here, then, we have several powerful drugs which can be used with great benefit against actinomycosis. We must now ask what place surgery has in treatment. The answer is—a diminishing sphere. Abscesses must be opened or, if small, aspirated. When the surgeon meets with a massive lesion of the stomach, intestine, or the kidney, excision of the affected part may be necessary. But now it is never needful to excise portions of lung or even to remove those masses of fibrous tissue which develop in this disease. In future visceral actinomycosis will be treated chiefly by the antibiotics, the sulphanilamide group of drugs,

iodine in some form, and perhaps X-rays to soften the hard tissue, while constitutional treatment will require full attention.

An extremely good illustration of what may be accomplished by modern treatment even in an advanced case is demonstrated in Fig. 9, which shows the complete disappearance of bilateral pulmonary actinomycosis which was treated by large doses of penicillin over the course of a year (under the care of Mr. Tubbs). An even more remarkable case was that of a patient under the care of Dr. Cawadias ; this was a man, aged 40, who developed a large hypogastric swelling which was diagnosed as inoperable malignant disease by a surgeon who explored the abdomen.



Fig. 9. Showing the effect of treatment of pulmonary Actinomycosis by penicillin.  
(Case under the care of Mr. Tubbs.)

Later a sinus formed and actinomycosis found. Large doses of penicillin caused a diminution of the mass, but a small faecal fistula formed and the liver became enlarged. A large actinomycotic abscess burst through the diaphragm from the liver, and both lungs became extensively involved by the disease. Several months' treatment by penicillin caused great improvement. The faecal fistula closed, the abdominal mass disappeared and the patient returned to his business in Athens. Soon after his return he developed Jacksonian fits and came back to England, where Sir Hugh Cairns completely excised an abscess in the left cerebral hemisphere. This abscess contained only diphtheroid organisms, but it is likely that any actinomycosis may have been destroyed by the treatment by the penicillin. Here, then, we have a case in which two, and probably all three, bodily cavities were seriously involved by actinomycosis, and yet a good recovery took place.

We have advanced far in the last 10 years but there remain many doubtful points to be solved in the pathology of actinomycosis. It was due to a distinguished Fellow of this College that treatment leaped forward ; I have the hope and faith to believe that some other Fellow of the College, perhaps some young doctor in this Hall, may be stimulated by what I have said to try to solve the problems which still remain.

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## SAYINGS OF THE GREAT

“Deep science is desirable to the man of fortune—useful science to the physician and surgeon.”—*Sir Astley Cooper*. (Submitted by Beric D. Stutter, F.R.C.S.)

“Every physician is prone to exaggerate the inveterate nature of the disease which he has cured.”—*Edward Gibbon*. (Submitted by Louis A. Ives, F.R.C.S.)

“Truth that has been merely learned adheres to us like an artificial limb, a false tooth, a waxen nose, or at best like one made out of another’s flesh; truth which is acquired by thinking for oneself is like a natural member; it alone really belongs to us.”—*Schopenhauer’s Essay on “Thinking for Oneself.”* (Submitted by F. A. Williamson-Noble, F.R.C.S.)

## 13TH CONGRESS OF THE INTERNATIONAL SOCIETY OF SURGERY

under the Presidency of Professor G. Grey Turner, F.R.C.S.

THE 13TH CONGRESS OF THE International Society of Surgery, held in New Orleans from October 10 to 15, was attended by some 500 participants, 45 countries being represented. All Europe, save Germany and Russia, sent delegates. As usual, France, Belgium, Spain and Italy were very well represented. Among the very large American group were many of the best-known surgeons, including Arthur Allen, Evarts Graham, Phemister, Collier, Lahey, Waltman Walters, Dragstedt, Naffziger and Parsons. The British contingent included Lambert Rogers, the representative on the International Committee, Ian Aird, Barrett, Rice Edwards, Frizelle, Loughridge, Mackey, Macnab, Reid, Sworn, Walters, Grey Turner and Lord Webb-Johnson. Of the Canadian Group, Gallie of Toronto was an outstanding figure.

Throughout the week the weather was trying, for it was both very hot and very humid with some heavy showers. The main activities were centred at the Roosevelt Hotel which was the headquarters and not far away from what might be called the medical centre, where the large Charity Hospital, with its great number of beds, was situated, the Medical Departments of the Tulane and Louisiana Universities adjoining.

A useful handbook in English, French and Spanish, was presented to those who registered, carrying portraits of the President and the venerable Professor Rudolph Matas, Honorary Chairman of the local committee, who is still hale and hearty at 89, and beloved as the doyen of the profession in the South, and the lode star of all medical and cultural activities in New Orleans.

The list of sponsors of the Congress was interesting and informative, for it included the State of Louisiana, the City of New Orleans, the Harbour Commissioners, International House, Association of Commerce, International Trade Mart, The Public Services Incorporation, as well as the Universities of Tulane and the Louisiana State. Our own public bodies might take notice of the practical interest extended to the Congress by circles outside the surgical world.

The people generally took a lively interest in the event, while newspaper publicity was keen and profuse, not only in New Orleans but in America generally. Everyone was kind and helpful and evidently imbued with a degree of civic pride which was refreshing.

The city is spread out over a large area with many wide boulevards leading to an extensive residential district. The open canals, such a marked feature of the original city, are now covered in and the recovered land is grass covered and bordered with trees.

Drainage and water supply are now good, and tropical fevers have been banished since 1905. That year marked the conquest over the "yellow jack" scourge, which had dominated the city for a century, and was a landmark of which medical science had so much reason to be proud.

The Inaugural function took place on the evening of the first day of the meeting at 8.30 p.m. and was quite a formal occasion, graced by the presence of the Hon. Walton Butterworth, an Assistant Secretary of State of the U.S.A., and the Hon. Earl K. Long, Governor of the State of Louisiana, the Mayor of the City and other civic representatives, the officers of the Society, the President of the American College of Surgeons, Dr. Sandblom of Stockholm, representing the delegates, and Lord Webb-Johnson representing our College.

Dr. Arthur Allen of Boston, as Vice-President of the Society, presided. At an early stage of the function the Mayor invested the President with the Honorary Citizenship of New Orleans and, in recognition, presented him with a golden key to the city. It was also at this function that Lord Webb-Johnson on behalf of the Royal College of Surgeons conveyed felicitations and presented a much appreciated message of congratulation. As there were 10 addresses to be made, more or less of a general and semi-political character, it was 10 o'clock before Professor Grey Turner, the President of the Congress, was called upon to give his inaugural address. The evening was hot and stuffy, and many in the audience must already have reached the point of weariness, if not of exhaustion. During the address the President showed lantern pictures of the presidents of the previous Congresses since the first, which was held in Brussels in 1905. The main theme of the address was on matters concerning the training of the surgeon, but in view of the late hour it had to be very considerably curtailed.

The scientific work began on Tuesday, an operative programme at Charity Hospital being billed from 7.30 a.m. to noon, the operations being televised to the ballroom of the Roosevelt Hotel. As the galleries at the hospital provided small accommodation for visitors, and as the floors of the theatres were occupied with many assistants, most people had perforce to be content with the television, which was generally agreed to be satisfactory. The screen was 8 ft. by 5 ft. ; the pictures were not in colour, but came out quite well ; however, only the immediate operative field could be seen, so that a grasp of the general topography was difficult.

There was a running commentary by the operator, relayed from the theatres, together with some interpolated remarks which were probably not intended to reach the air !

The televising of other operative sessions was also conducted on the Thursday. Professors Rives, Alton Ochsner, Maes and others were the operators.

The scientific discussions commenced on Tuesday afternoon, when Professor Paolucci of Rome gave the opening paper on the Surgery of the Parathyroids. In the discussion Leriche of Paris, Bastos-Ansart of Barcelona, Parsons of New York, Jung and Fontaine of Strasbourg, Mallet-Guy of Lyons, Manzarilla of Mexico, and others took part.

Each opening speaker was allowed 30 to 40 minutes, subsequent speakers only five, but it was really remarkable that, due to the exertions of

the President in the Chair, the speakers kept pretty well to this schedule. Another feature of the Congress was the installation of the headphone transmission which worked well enough to give great hopes for its complete success in the future. By adjusting the apparatus, each member of the audience could elect to listen to the speaker in the language employed, or to hear a translation into French or Spanish. If interpreters familiar with technical terms are available, the rendering is naturally better.

The next session on the Surgery of the Pancreas was opened auspiciously by Professor Ian Aird of London, assisted by an excellent series of lantern slides with captions in French. He dealt mainly with operative procedures and gave a detailed account of the exposure of the organ. In the discussion most aspects of the subject were dealt with by speakers from Mexico, Sweden, Bulgaria, North Africa, France and the United States.

The discussion on Post-Operative Thrombosis and its sequelæ was opened by Alton Ochsner of New Orleans and De Bakey of Houston, and their remarks were supported by imposing statistics graphically presented on the screen. There was a lively discussion, joined by nearly two dozen speakers, representing surgical experience from many parts of Europe as well as America. Lambert Rogers stressed the importance of prophylaxis and urged that the calves should not be allowed to press on the table throughout long operations. Three points came out very clearly: (1) that these conditions were still a serious menace in surgical practice; (2) that early rising after operation had not reduced the incidence; (3) that no one method of treatment was generally agreed.

Surgery of the Pituitary was dealt with by Paul Martin of Brussels in what was generally regarded as a masterly contribution, covering the subject so well that there was very little not touched upon. Naffziger, himself an acknowledged authority, congratulated the speaker on his complete presentation.

The Suprarenal Glands were dealt with by Fontaine of Strasbourg, who emphasised the prominent part played by his great master, Leriche, in the development of the subject. As he warmed to his task the speaker's eloquence increased, and it was obvious that in concluding after a good innings, there was still much he would have liked to say! There was quite a good international discussion, but without any special pronouncement.

The evening session at 7.30 was devoted to the causes of the recurrences after operation on the Biliary Tract. The opening by Demel of Vienna was delivered in German and was characteristically emphatic and thorough. It was a great effort, a *tour de force* much appreciated by those who understood German or who had read the translation thoughtfully provided by the Secretariat. Some latitude to the earlier speakers in the discussion gave an opportunity to Lahey of Boston, Mirizzi of Cordoba, Mallet-Guy of Lyons and Pribram of New York to illustrate their remarks by a fine show of lantern slides. Lahey, with his large experience to draw upon, condemned all methods of intubation and was in favour of a deliberate search for the distal part of the duct followed by end-to-end anastomosis and claimed that this plan gave far the best results. Later in the discussion

the President drew attention to the serious reproach to surgery provided by the large numbers of cases in which these injuries had followed deliberate surgical intervention. He stated emphatically the necessity for constantly stressing the importance of prophylaxis. The session came to an end about 11 o'clock after a large number of speakers had made their contributions.

Friday and Saturday were devoted to the presentation of a long series of 15-minute papers by the younger American surgeons. This session had been arranged by the American branch of the International Society as an experiment and as an offset to the rather senior tendency in the general discussions. Though many of the communications were of great interest and importance, 12 papers before luncheon and 12 thereafter was rather a severe strain and a concentrated mental effort for all concerned !

There was a great variety of subjects many dealing with experimental surgery on purely advanced physiology.

Several members agreed with the President, who, while extolling the experiment, suggested that it would have been more useful if there had been rather fewer presentations with time for questions and limited discussion.

The scientific meeting came to an end about 3 o'clock on Saturday afternoon and brought a strenuous week to a happy conclusion.

On Wednesday morning, starting at 8, visits were made to the two Schools of Medicine, which occupy adjoining premises and share their clinical work in the neighbouring Charity Hospital.

Each of these institutions is splendidly equipped both for teaching and research, and signs of keen activity and perhaps some rivalry were apparent. At Tulane a special visit was paid to the Matas Library, where an interesting ceremony was carried out in honour of that surgeon, who for so long has done so much for the School. The President, Professor Grey Turner, told the company something of the work of Dr. Matas and how much he was admired and respected in England. He also spoke of the uses of a medical library and especially urged his younger listeners to follow the example of the doyen by the study of medical history, not only for its interest, but as an assistance to the work in their immediate studies, and as a guide to the future. Dr. Matas made a feeling reply. At this ceremony Professor Grey Turner was presented with an inscribed silver plaque to commemorate the occasion, and in honour of Dr. Matas.

Of the social functions, a harbour trip on the first day, on a spacious river steamer, with luncheon aboard, proved a good way of getting visitors and hosts to meet and of breaking the ice. The evening reception in honour of the President, held at one of the fine country clubs, was delightful. On that occasion the provision of transport from the town and back was a thoughtful and helpful arrangement.

The closing banquet held at the Roosevelt Hotel on Friday night was also a colourful and enjoyable function. The top tables raised on a dais were unusual and certainly gave after-dinner speakers a commanding



Fig. 1. Professor Rudolf Matas and Professor Grey Turner after presentation of a silver plaque in the Matas Library at Tulane University.

position. The President occupied the Chair, and his call for the health of the President of the United States, followed by the Stars and Stripes, was a fitting compliment to our kind hosts, but this was returned when the orchestra played some bars of God Save the King. There was no formal toast list but several speakers were called upon to unburden themselves of appropriate messages. There was tremendous applause when Professor Rudolf Matas came to the loudspeaker, and, despite his years, the choice was justified for he spoke audibly and entertainingly in English, French, Spanish and Italian. At the conclusion of his speech there was a moving scene when the Chairman took him by both hands, and said: "Professor Matas, the assembled company, the International Society, and the whole World of Surgery, salute you."

At the General Assembly of the Society, which once again was presided over by the mature Professor Jan Verhoogen, several important decisions were made, for it was agreed that with certain precautions, both German and Japanese surgeons should again be received into the Society. A Committee was appointed to make suggestions on the reorganisation of the Journal. The officers and various committees were re-elected. It was also decided that the next Congress, the 14th, should be held in Paris in October, 1951, and Professor Rene Leriche of that city was elected President.



## "OBSERVABLES" AT THE ROYAL COLLEGE OF SURGEONS

### 24. CLOCKS

THE MOST HISTORIC and probably the oldest of the clocks in the possession of the College is that which was once John Hunter's. It is a pendulum clock, with strike, and was made by William Hughes of High Holborn. Its back plate of brass is engraved with a pleasing design of flowers, a basket of fruit, scroll work and the maker's name. The two inscriptions engraved on the base show the outlines of the clock's history: "This Clock formerly belonging to John Hunter was left by his widow to Matthew Baillie, M.D., Jan. 7th 1821" and "Presented to the Royal College of Surgeons of England by the family of Mr. W. Hunter Baillie, son of Dr. Matthew Baillie, 1895." Until the 1939 war this clock was in the Council Room and now stands in the President's Room.

Other clocks have been longer in the College, notably that in Room I of the Museum. This was presented no less than 184 years ago by Mr. John Townsend who had been Master in 1762. The Court of Assistants on 17th January, 1765, resolved "That the thanks of this Court be now given to Mr. Townsend for his Genteel present of a Clock for the use of the Company," and the clock bears the inscription "The gift of Mr. Jno. Townsend." Early records show that this clock was at one time in the Committee Room and later the Secretary's office, and it may well have been in its present position since the room was built in 1891.

The College bought clocks from "Mr. French" for £18 18s. 0d. in June, 1824, and for £31 10s. 0d. in December, 1827, and one of these must be the grandfather clock which stands in the Secretary's office. This is a regulator clock, having a separate inset dial for the hour hand, as well as the second hand, and being thereby a source of temporary bewilderment to strangers. It narrowly escaped destruction in 1940 when an iron bar, intended to secure the window shutters, was hurled across the room by the action of a land mine and broke the door of the clock case into two pieces.

The bracket clock in the Librarian's Room is by Payne, of 163, New Bond Street, and looks interesting, but its history is unrecorded except for the fact that it has been in the Library at least since 1880.

The clock with a marble plinth which is depicted in the examination portrait group in the Dining Room had been in the College at least since 1880 and was destroyed by enemy action in 1941.

The Dining Room clock was presented to the College in 1914 by Mrs. Mary Fifield King, of Milton, Massachusetts, in memory of her father, William Cranch Bond Fifield, M.R.C.S., of Boston (1828-1896).

The Library clock (by Asprey) seems to have been purchased for £28 10s. 0d. from G. W. Blackie in 1889, when the Library was enlarged.

A bequest of furniture from Lady Bland-Sutton in 1943 provided much needed replacements, notably the bracket clock in the Council Room (which has two sets of chimes) and the grandfathers in the Residential College and the Joint Secretariat.

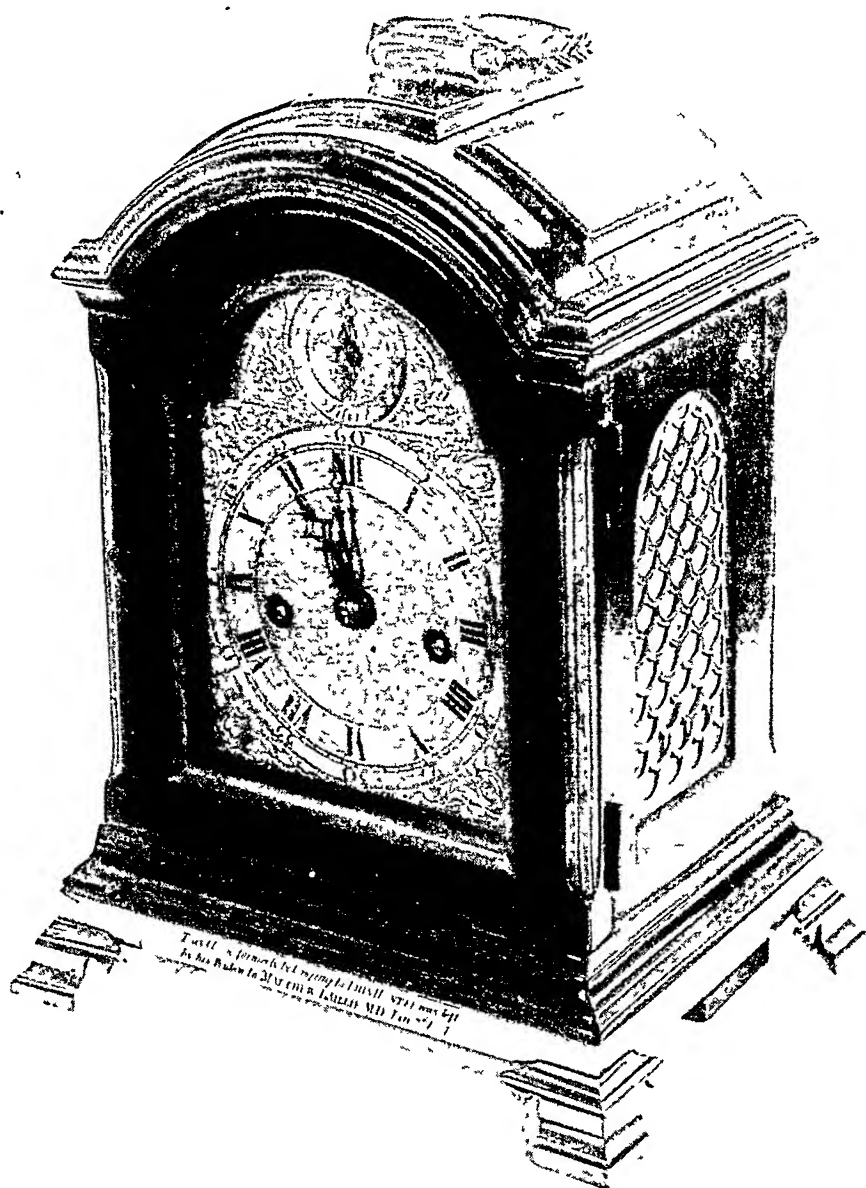


Fig. 1. JOHN HUNTER'S CLOCK.

Presented to the Royal College of Surgeons of England by the family of Mr. W. Hunter Baillie, son of Dr. Matthew Baillie (1895).

## THE LIBRARY

James Cooke and his "Marrow of Surgery."

THE COLLEGE HAS acquired lately two rare editions of books by James Cooke, whose *Marrow of Surgery* was the most popular English surgical textbook of the second half of the seventeenth century. The Library now has the series of editions of his work, except for the first. That was published in 1648, towards the end of the first Civil War, in which Cooke served as a Surgeon with the Parliamentary Army. Cooke was a Warwickshire man, and in 1642 he was stationed at Stratford on Avon. Here he came to know the widow of Dr. John Hall who had practised at Stratford for many years, and from her he bought some of Hall's manuscripts.

"Being in my Art an Attendent to parts of some regiments to keep the pass at the Bridge of Stratford upon Avon, There being then with me a Mate allyed to the Gentleman that writ the following Observations in Latin"—Cooke thus opens the preface to his translation of Hall's case-books—"he invited me to the house of Mrs. Hall, Wife to the deceased, to see the Books left by Mr. Hall. After a view of them, she told me she has some Books left by one, that professed Physick, with her Husband for some mony. I told her if I liked them I would give her the mony again; she brought them forth, amongst which there was this with another of the Author's, both intended for the Presse. I being acquainted with Mr. Hall's hand, told her that one or two of them were her Husband's and shewed them her; she denied, I affirmed, till I perceived she begun to be offended. At last I returned her the mony."

Now Mrs. Hall was Shakespeare's daughter Susannah, and it is possible to speculate from this story whether she showed Cooke any of her father's writing, and from her ignorance of her husband's hand whether she could read. Be that as it may, Cooke took advantage of his purchase and later published a selection from Hall's manuscript, the story of which must be left for another occasion.

First, however, he had published his own textbook *Mellificium chirurgiae or the marrow of many good authors* 1648. The prefatory address "To the young Chirurgion" is dated from Warwick, March 1, 1647. This book was reissued with the authority of the College of Physicians in 1662, after the Restoration of King Charles II. Cooke describes himself as "Practitioner in Physick and Chirurgery," and his book is in fact not merely surgical but a handbook for the general practitioner. He defines "Physick" as having "two generall parts: First, Theory, which gives Axiomes officious to make inquest into the various disposition of the subject, by what Symptomes they may be apprehended; hence flowes three parts: Physiologia, Pathologia, and Semeiotica, which are speculative. Secondly, Practick, which hath two parts: Hygieticke, to preserve health, and Therapeutick, to cure diseases."

The contents of the book comprise these special subjects under the general heading of "Institutions," followed by "Hippocrates Aphorismes"

in classical order with comment," "Receipts," (we shall here set down some very good Receipts approved by several persons of note), and finally, filling more than half the little volume, "The Art of Chirurgery" in four books. Cooke summarizes the purpose of this "second part of the curative part of medicine" as being: "First, To unite parts disjoyn'd. Secondly, To separate such unnaturally joyn'd. Thirdly, To remove things superfluous. Fourthly, To supply things wanting."

Between the first and second editions Cooke had published in 1655 his *Supplementum Chirurgiae, or the Supplement to the Marrow of Chirurgerie, wherein is contained Fevers, Simple and Compound, Pestilential and not, Rickets, Small Pox and Measles, as also the Military Chest*. A copy of this rare Supplement has lately come to the College Library.

The chapter on Rickets, some 40 pages long, is of much interest in itself and has some claim to be one of the earliest accounts of the disease. Cooke says that he had read of this new disease "in print in a Thesis long before the Doctors Tract on the subject." He names no authors, but says that the disease was called "Paedesplanchnosteocaces" in this Thesis, and "Rachitis" by the Doctors (i.e., the College of Physicians), showing that he had in mind Daniel Whistler's Leyden thesis of 1645 and Francis Glisson's *Tractatus de Rachitide* of 1650, and he suggests in his preface that his own account of rickets had been written before Glisson's was published.

By a separate acquisition a fine copy of the rarest of Cooke's books, the third edition of the *Marrow of Surgery* 1676, has been obtained in recent months. For this edition the book was increased in format and content, as Cooke's new title-page shows:

*Mellificium Chirurgiae or the Marrow of Chirurgery much enlarged, to which is now added Anatomy, illustrated with twelve Brass Cuts, and also the Marrow of Physick: Both in the newest way.* Besides the miscellaneous contents of the earlier editions and the new sections specially named in the title, the matter from the Supplement of 1655 has been rewritten and incorporated in three extra books of the Surgery section.

Besides the "Brass Cuts," which include anatomical schemata deriving from Vesalius and illustrations of surgical instruments, there is a portrait of Cooke aged 64 by R. White. It is a beautiful engraving and shows him as a handsome and courtly man in a formal full wig. White's second portrait of him at the age of 71, included in the 1685 edition of the *Marrow of Surgery*, shows him without his wig, and we may guess it to be more characteristic of the old Roundhead army surgeon of 40 years earlier.

Cooke died in 1688 and was buried in St. Mary's Church, Warwick. This church was burned down six years later, and if there was a monument to him it disappeared then. Thomas Gibson, physician and anatomist, brought out further editions of the *Marrow of Surgery* in 1693 and 1717; these like that of 1683 reproduce the contents of the enlarged edition of 1676. Gibson's own *Anatomy of humane bodies epitomized* was as popular in its field as Cooke's *Marrow of Surgery*.

W.R.L.F.

## MONTHLY DINNERS

Monthly dinners are held in the College on the Wednesday before the second Thursday of each month. The following are entitled to attend with their guests : All Diplomates and students of the College and Members of the Associations linked to the College through the Joint Secretariat. It is not necessarily intended that guests should be members of the medical profession.

The dinners will be at 7 p.m. on the following Wednesdays : January 11, February 8, March 8, April 12, May 10, and June 7, 1950. There is an inclusive charge of £1 5s. (including drinks), which must be sent with the application to the Assistant Secretary at least a week before the date of the dinner. The dress is Lounge Suit or Uniform.

### DIARY FOR DECEMBER (15th-30th)

Thur. 15		Pre-Medical Examination begins.
	3.45	PROF. J. BEATTIE—Peripheral Autonomic System.
	5.00	DR. A. HUXLEY—Central Nervous System.
Fri. 16		D.L.O. Examination (Part II) begins.
Mon. 19	3.45	PROF. J. BEATTIE—Peripheral Autonomic System.
	5.00	DR. H. F. BREWER—Hæmatology.
Tues. 20	5.00	MR. R. J. LAST—Arnott Demonstration.*
Wed. 21	3.45	PROF. J. D. BOYD—Development of the Pharyngeal Derivatives and Endocrine Glands.
	5.00	DR. A. HUXLEY—Central Nervous System.
Fri. 23		College Closed.
Wed. 28		College reopens.
Thur. 29	3.45	PROF. T. NICOL—Applied Anatomy of the Thorax.
	5.00	DR. A. HUXLEY—Central Nervous System.
Fri. 30		D.P.H. Examination (Preliminary) begins.
	3.45	PROF. T. NICOL—Applied Anatomy of the Kidneys, Ureter and Bladder.
	5.00	DR. H. D. ROSS—(Subject to be announced).

\* Not part of courses.

### DIARY FOR JANUARY

Mon. 2	3.45	PROF. J. BEATTIE—Autonomic Centres of the Brain Stem and Diencephalon.
	5.00	DR. H. F. BREWER—Hæmatology.
Tues. 3		Final Membership Examination begins.
	5.00	MR. C. E. SHATTOCK—Erasmus Wilson Demonstration.
Wed. 4	3.45	PROF. J. WHILLIS—The Tongue and Palate.
	5.00	DR. H. F. BREWER—Hæmatology.
Thur. 5		D. P. H. Examination (Final) begins.
	3.45	PROF. J. WHILLIS—The Pharynx.
	5.00	DR. H. D. ROSS (Subject to be announced).
Fri. 6	3.45	PROF. J. BEATTIE—The Hypothalamic Control of Autonomic Function.
	5.00	MR. C. E. SHATTOCK—Erasmus Wilson Demonstration.
Tues. 10	5.00	MR. P. H. MITCHINER—Erasmus Wilson Demonstration.
Wed. 11	5.00	MR. L. W. PROGER—Erasmus Wilson Demonstration.
Tues. 17	5.00	MR. F. DOUGLAS STEPHENS—Arris and Gale Lecture.
Wed. 18	5.00	MR. D. F. ELLISON NASH—Arris and Gale Lecture.
Fri. 20		Board of Faculty of Dental Surgery.
	5.00	MR. P. H. MITCHINER—Erasmus Wilson Demonstration.
Mon. 23		Basic Sciences Lectures and Demonstrations for Dental Students begin.
Tues. 24	5.00	MR. L. W. PROGER—Erasmus Wilson Demonstration.
Wed. 25		Primary F.R.C.S. Examination begins.
Mon. 30		Final L.D.S. Examination (Part I) begins.

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